# Clinical efficacy of decitabine-containing induction chemotherapy in *de novo* non-elderly acute myeloid leukemia

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**Abstract.** To improve the complete response rate (CRR) and reduce the recurrence rate of newly diagnosed non-elderly acute myeloid leukemia (AML), the present study compared the clinical efficacy of decitabine with cytarabine (A) and daunorubicin (D)-based remission induction therapy with D + A-based remission induction therapy. A total of 81 patients with newly diagnosed non-elderly AML (non-M3) were enrolled in the present study, and divided into the observation group [decitabine with D + A, demethoxydaunorubicin (I) + A or homoharringtonine (H) + A] and the control group (D + A, I + A or H + A). The observation group displayed a 91.4% CRR [95% confidence interval (CI), 81.7-100%] and the control group displayed a 69.6% CRR (95% CI, 55.8-83.4%). The 2-year overall survival (OS) rate was improved in the observation group compared with the control group (P=0.008). Patients aged <60 years displayed a 92.9% CRR in the observational group and a 71.1% CRR in the control group (P<0.05). Patients with undetected methylation gene mutations displayed an improved CRR in the observation group compared with the control group (92.9 vs. 71.4%; P=0.028). Furthermore, relapse-free survival (P=0.041) and OS (P=0.007) were significantly extended in the observation group compared with the control group. The present study suggested that the administration of decitabine with DA, IA or HA as an induction therapy improved the clinical efficacy and reduced the recurrence rate in patients with AML.

## Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with an yearly incidence of 5.5 per 100,000 population, and a mortality of 55.5% in the United States (1). The incidence of AML increases with age, with a 5-year survival rate of 26.6% in the United States (1-3). The conventional chemotherapy regimen for AML is the daunorubicin (D) + cytarabine (A) '7+3' modality (A treatment for 7 days combined with D treatment for 3 days; 3 days of combined treatment followed by a further 4 days of A), which can achieve complete remission (CR) in 60-80% of adult patients (4); however, most patients inevitably experience recurrence. Furthermore, 20-30% of newly diagnosed patients do not achieve CR (4-6). Therefore, there is an urgent requirement to introduce a novel effective induction modality into the clinic to increase the CR rate (CRR) and reduce the recurrence rate to improve long-term survival.

Previous studies have reported that AML is caused by pre-leukemia hematopoietic stem cells (pre-HSCs) that do not respond to chemotherapy and lead to disease relapse (7-9). In addition, pre-HSCs carry mutations in DNA methylation genes, including DNA methyltransferase 3α (DNMT3A), tet methylcytosine dioxygenase 2 (TET2) and isocitrate dehydrogenase isozyme (IDH)1/2, which can persist from AML initiation to relapse (7-9). Whole-genome hypermethylation is associated with poor clinical outcome, and gene promoter-specific hypermethylation is an important step in tumor development during AML (10). However, DNMT3A is associated with hypomethylation, whereas TET2 and IDH1/2 display global and gene-specific hypermethylation during AML (11,12). Therefore, studying the efficacy of demethylation drugs in patients with AML is crucial.

The demethylating drug decitabine, a natural adenosine analogue of 2'-deoxycytidine, reduces DNA methylation by inhibiting DNA methyltransferase (6). Decitabine inhibits tumor cell proliferation and prevents drug resistance. As mutations in DNA methylation genes persist from initiation to relapse, decitabine may improve the clinical efficacy against AML by reducing the frequency of DNA methylation (3). Recent studies have suggested that decitabine can improve the remission rate of elderly patients with AML (3,4,13). However, it has not been reported whether decitabine is beneficial in younger patients or reduces the recurrence rate of AML. Therefore, in the present study, the therapeutic effects of decitabine in combination with the DA induction modality in *de novo* non-elderly patients with AML were investigated.

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*Key words:* acute myeloid leukemia, decitabine, demethylation

## Materials and methods

*Patients*. A total of 81 patients with *de novo* AML (non-M3) who received D + A or equivalent modalities [D + A, demethoxydaunorubicin (I) + A or homoharringtonine (H) + A] with or without decitabine as induction chemotherapy were recruited retrospectively between January 2017 and December 2018 at Huazhong University of Science and Technology Affiliated Tongji Hospital. AML was diagnosed according to the criteria of the World Health Organization (WHO) (14) and French-American-British (FAB) classification (15). Inclusion criteria were as follows: i) Aged 14-65 years; ii) patients with AML (non-M3) with clear diagnosis meeting the WHO 2008/2016 standard and FAB classification; iii) newly diagnosed AML after January 1st 2017; iv) received ≥2 courses of D + A, I + A or H + A modalities with or without decitabine (20 mg/m$^2$/d) for 5 days; and v) an Eastern Cooperative Oncology Group (ECOG) score ≤2 points. Exclusion criteria were as follows: i) Allergic to decitabine; ii) patients who had a previous AML diagnosis; iii) transformation of myelodysplastic syndrome (MDS) or other hematological diseases, including bone marrow fibrosis; iv) central nervous system invasion; v) other serious diseases, including myocardial infarction, severe or unstable angina, severe arrhythmia or cerebrovascular events (including transient cerebral ischemia); and vi) <2 courses of treatment, or treatment efficacy not assessed. The present study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology and was conducted in accordance with the Declaration of Helsinki. Written informed consent was not obtained from the patients, as the Ethics Committee approved the application for exemption of informed consent. All patients received follow-up at the clinic or via a telephone call. The span of follow-up time was 24 months (median, 10 months; range, 1-24 months).

The present study recruited 43 male and 38 female patients (male:female, 1.13:1; age, 14-71 years). The observation group (decitabine with D + A, I + A or H + A modalities) consisted of 35 patients, and the control group (D + A, I + A or H + A modalities without decitabine) consisted of 46 patients. The ECOG performance status score ranged from 0 to 2. No significant differences in sex, age, blood cell count or organ function were identified between the two groups.

*Study design and treatment*. Patients with leukocytosis were treated with hydroxyurea or A to reduce leukocyte counts to ≤50x10$^9$/l prior to initiation of induction therapy. Risk stratification was determined by cytogenetics and molecular aberrations according to the National Comprehensive Cancer Network and European Leukemia Net criteria (16,17). After 1-2 cycles of treatment, the initial response was evaluated. Post-remission treatment included consolidation of intensive therapy and/or HSC transplantation. Patients who achieved CR or partial remission (PR) after 1-2 courses of induction chemotherapy were treated with the original regimen, medium dose A as consolidation therapy or transplantation. The efficacy of consolidation therapy was comparable between the two groups. Follow-up was continued until relapse. The specific induction schemes were as follows: i) The observation group received decitabine with D + A (14 patients), I + A (16 patients) or H + A (5 patients) modalities, and the control group received D + A (17 patients), I + A (20 patients) or H + A (9 patients) modalities. The specific protocol for the observation group was as follows: Decitabine (20 mg/m$^2$/day) for 5 days + A (100-200 mg/m$^2$/day) for 7 days + D (60 mg/m$^2$/day) for 3 days, I (10 mg/m$^2$/day) for 3 days or H (3 mg/m$^2$/day) for 7 days. The specific protocol for the control group was as follows: A (100-200 mg/m$^2$/day) for 7 days + D (60 mg/m$^2$/day) for 3 days, I (10 mg/m$^2$/day) for 3 days or H (3 mg/m$^2$/day) for 7 days.

*Response criteria and outcome evaluation*. The following conditions were defined according to the International Working Group criteria (18). CR was defined as <5% bone marrow blasts, no blasts with Auer rods, the absence of extramedullary disease, an absolute neutrophil count >1.0x10$^9$/l or a platelet count ≥100x10$^9$/l. PR was defined as a ≥50% decrease (5-25%) in the frequency of blasts detected in bone marrow aspirates and normalized blood counts. Overall remission rate (ORR) was calculated as the sum of CR + PR. Non-remission was defined as a response that had achieved neither CR nor PR. Relapse was defined as the reappearance of leukemia cells in the peripheral blood or >5% blasts in the bone marrow. Overall survival (OS) was defined as the time from diagnosis to death or the follow-up deadline. Recurrence-free survival (RFS) was defined as the period between remission by induction chemotherapy and relapse or death. The follow-up deadline was December 30th 2018.

*Statistical analysis*. Statistical analyses were performed using SPSS (version 20.0; IBM Corp.) and GraphPad Prism (version 7.0; GraphPad Prism, Inc.) software. Data are expressed as the mean ± standard deviation. Comparisons were performed using Student's t-test. Categorical data were compared using $\chi^2$ test, $\chi^2$ test with correction for continuity or Fisher's exact test as applicable. The Kaplan-Meier method was used to plot survival curves and survival data (RFS and OS probability) were analyzed by the log-rank test. P<0.05 were considered to indicate statistically significant differences.

## Results

*Patient characteristics*. A total of 81 patients were included in the present study, including 43 male and 38 female patients. The median age of the patients was 58.5 years (age range, 14-71 years). The observation group consisted of 35 patients and the control group consisted of 46 patients. There were no significant differences in sex, age or peripheral blood cell count between the two groups (P>0.05). The adverse effects of each group were compared, and no significant differences were observed. Patient characteristics are summarized in Tables I and II.

*Response to induction therapy*. In the observation group, 32 patients achieved CR and 3 patients achieved PR. The observation group displayed a 91.4% CRR (95% CI, 81.7-100%) and 100% ORR (95% CI, 100-100%). In the control group, 32 patients achieved CR and 7 patients achieved PR; therefore, the CRR was 69.6% (95% CI, 55.8-83.4%) and the ORR was 84.8% (95% CI, 74-95.6%). Significant differences in CRR

Table I. Clinical characteristics of patients with acute myeloid leukemia.

A, Favorable risk

| Characteristics | Control group | Observation group | P-value |
|---|---|---|---|
| Sex | | | >0.999 |
| Male | 2 | 2 | |
| Female | 4 | 2 | |
| Age, years, median (range) | 37 (22-46) | 37 (22-70) | 0.519 |
| WBC count, x$10^9$/l | | | |
| Mean ± SD | 20.23±11.23 | 14.81±10.30 | 0.462 |
| Median (range) | 22.06 (2.32-26.15) | 15.66 (1.63-26.29) | |
| Hb, g/l | | | |
| Mean ± SD | 71.33±18.80 | 56.75±7.19 | 0.183 |
| Median (range) | 62.50 (57.00-106.00) | 57.50 (48.00-64.00) | |
| PLT, x$10^9$/l | | | |
| Mean ± SD | 36.00±13.27 | 28.50±11.45 | 0.384 |
| Median (range) | 36.50 (15.00-54.00) | 30.50 (13.00-40.00) | |

B, Intermediate risk

| Characteristics | Control group | Observation group | P-value |
|---|---|---|---|
| Sex | | | 0.949 |
| Male | 18 | 14 | |
| Female | 12 | 9 | |
| Age, years, median (range) | 39 (14-66) | 43 (15-63) | 0.791 |
| WBC count, x$10^9$/l | | | |
| Mean ± SD | 48.22±62.47 | 52.41±104.77 | 0.861 |
| Median (range) | 17.085 (1.22-232.83) | 10.09 (0.38-486.69) | |
| Hb, g/l | | | |
| Mean ± SD | 82.89±20.41 | 76.91±16.16 | 0.266 |
| Median (range) | 84.00 (43.00-127.00) | 75.50 (51.00-105.00) | |
| PLT, x$10^9$/l | | | |
| Mean ± SD | 52.64±41.09 | 68.27±60.50 | 0.306 |
| Median (range) | 38.5 (4.00-205.00) | 39.00 (2.00-219.00) | |

C, Unfavorable risk

| Characteristics | Control group | Observation group | P-value |
|---|---|---|---|
| Sex | | | >0.999 |
| Male | 4 | 3 | |
| Female | 6 | 5 | |
| Age, years, median (range) | 39 (30-57) | 55.5 (28-71) | 0.081 |
| WBC count, x$10^9$/l | | | |
| Mean ± SD | 25.81±30.82 | 32.65±46.48 | 0.713 |
| Median (range) | 17.48 (4.43-104.55) | 9.51 (0.45-133.19) | |
| Hb, g/l | | | |
| Mean ± SD | 80.30±20.68 | 93.00±34.45 | 0.356 |
| Median (range) | 79.50 (49.00-110.00) | 76.00 (67.00-153.00) | |
| PLT, x$10^9$/l | | | |
| Mean ± SD | 59.20±40.93 | 41.00±23.62 | 0.309 |
| Median (range) | 46.50 (16.00-136.00) | 35.00 (16.00-82.00) | |

Hb, hemoglobin; PLT, platelet; WBC, white blood cell.

Table II. Clinical characteristics of patients with acute myeloid leukemia.

| Characteristics | Observational group, n (%) | Control group, n (%) |
|---|---|---|
| Sex | | |
| Male | 19 (54) | 24 (52) |
| Female | 16 (46) | 22 (48) |
| Age | | |
| Median (range) | 55 (15-71) | 49 (14-66) |
| FAB classification | | |
| M0 | 1 (3) | 0 (0) |
| M1 | 2 (6) | 5 (11) |
| M2 | 11 (30) | 13 (28) |
| M4 | 4 (11) | 8 (17) |
| M5 | 16 (47) | 20 (44) |
| M7 | 1 (3) | 0 (0) |
| Gene mutation | | |
| Methylation | | |
| DNMT3A | 4 (11) | 2 (4) |
| TET2 | 1 (3) | 1 (2) |
| IDH2 | 2 (6) | 3 (7) |
| Non-methylation | | |
| NPM1 | 2 (6) | 3 (7) |
| CEBPA | 7 (20) | 12 (26) |
| FLT3-TKD | 1 (3) | 2 (4) |
| FLT3-ITD | 6 (17) | 7 (15) |
| CBFβ-MYH11 | 4 (11) | 5 (11) |
| AML1-ETO | 4 (11) | 7 (15) |
| C-kit | 2 (6) | 10 (22) |
| NUP98-HOX11 | 1 (3) | 0 (0) |
| ASXL1 | 0 (0) | 1 (2) |
| EZH2 | 0 (0) | 1 (2) |
| DEK/CAN | 0 (0) | 1 (2) |
| MLL | 3 (9) | 4 (9) |
| Cytogenetics | | |
| t(8;21) | 3 (9) | 8 (17) |
| inv(16) | 4 (11) | 5 (11) |
| Complex karyotype | 1 (3) | 1 (2) |
| Risk stratification[a] | | |
| Favorable | 4 (11) | 6 (13) |
| Intermediate | 23 (66) | 30 (65) |
| Unfavorable | 8 (23) | 10 (22) |
| Allo-HSCT | 4 (11) | 6 (13) |
| Adverse event[b] | | |
| Febrile neutropenia (grade 3-4) | 15 (43) | 19 (1) |
| Abdominal pain (grade 2) | 0 (0) | 1 (2) |
| Oral pain (grade 2) | 0 (0) | 1 (2) |
| Vomiting (grade 1-2) | 10 (29) | 14 (30) |
| Multi-organ failure (grade 3) | 0 (0) | 1 (2) |
| Gallbladder infection (grade 3) | 1 (3) | 0 (0) |
| Lung infection (grade 3-4) | 8 (23) | 14 (30) |
| Skin infection (grade 2-3) | 2 (6) | 2 (4) |
| Sepsis (grade 4) | 1 (3) | 1 (2) |

[a]According to National Comprehensive Cancer Network guideline of acute myeloid leukemia (2016); [b]According to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. Allo-HSCT, allogenic hematopoietic stem cell transplantation.

Table III. Comparison of efficacy between control and observation groups.

| Group | N | CR | PR | NR | CR, % | ORR, % |
|---|---|---|---|---|---|---|
| Observation group | 35 | 32 | 3 | 0 | 91.4 | 100 |
| Control group | 46 | 32 | 7 | 7 | 69.6 | 84.8 |

CR, complete remission; NR, no remission; ORR, overall remission rate; PR, partial remission.

Table IV. Comparison of efficacy between the two groups stratified by favorable risk, intermediate risk and unfavorable risk.

| Risk group | CR (%) | Non-CR (%) |
|---|---|---|
| Favorable risk | | |
| Observation group | 4 (100) | 0 (0) |
| Control group | 5 (83.3) | 1 (16.7) |
| Intermediate risk | | |
| Observation group | 21 (91.3) | 2 (8.7) |
| Control group | 21 (70) | 9 (30) |
| Unfavorable risk | | |
| Observation group | 7 (87.5) | 1 (12.5) |
| Control group | 6 (60) | 4 (40) |

CR, complete remission.

and ORR were identified between the observation and control groups (P=0.017 and P=0.044, respectively; Table III).

Based on cytogenetic abnormalities and molecular mutations, 81 *de novo* patients with AML were stratified into favorable risk, intermediate risk and unfavorable risk groups (Table IV). For patients with intermediate and unfavorable genetic aberrations, the observation group displayed an improved CRR compared with the control group (90.3 vs. 67.5%, respectively; P=0.022; Fig. 1). In patients without methylation gene mutations, the CRR was improved in the observation group compared with the control group (92.9 vs. 71.4%, respectively; P=0.028; Fig. 2).

According to patient age, patients were grouped into <60 and ≥60 years groups. The observation group consisted of 28 patients aged <60 years and the control group consisted of 45 patients aged <60 years. The ORR did not differ significantly between the observation and the control groups (100 vs. 84.4%, respectively; P=0.074); however, the CRR was improved in the observation group compared with that in the control group (92.9 vs. 71.1%, respectively; P=0.025; Fig. 3).

*OS and RFS*. Among the 81 patients, 9 developed recurrence during follow-up, including 2 patients in the observation group (5.7%) and 7 patients in the control group (15.2%). The recurrence rate curves of the two groups are presented in Fig. 4. Although the 2-year recurrence rate was similar between the two groups (P>0.05), the 2-year OS rate was improved in the

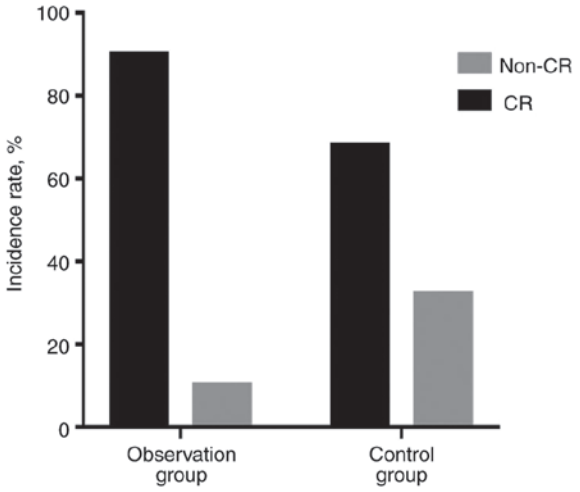


Figure 1. Comparison of CR in patients with intermediate and unfavorable risk between the two groups. The y-axis represents the incidence rate. For patients with intermediate and unfavorable risk, the observation group consisted of 28 patients with CR (90.3%) and the control group consisted of 27 patients with CR (67.5%). The non-CR rates were 9.7 and 32.5% for the observation and control groups, respectively. P<0.05. CR, complete remission.

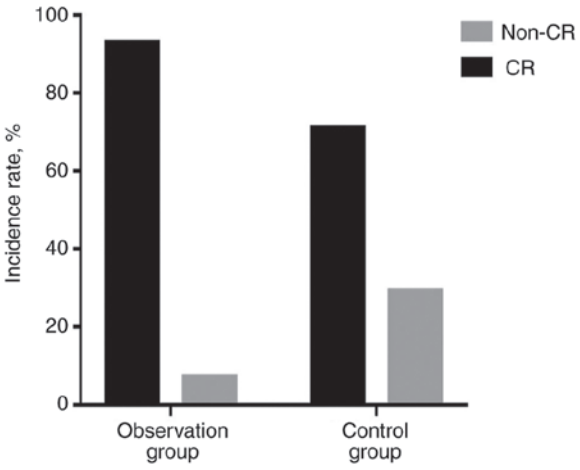


Figure 2. Comparison of CR in patients with undetected methylation gene mutations between the two groups. The y-axis represents the incidence rate. For patients with undetected methylation gene mutations, the observation group consisted of 26 patients with CR (92.9%) and the control group consisted of 30 patients with CR (71.4%). The non-CR rates were 7.1 and 28.6% for the observational and control groups, respectively. P<0.05. CR, complete remission.

observation group compared with that in the control group (P=0.008). The OS curves of the two groups are presented in Fig. 5. The 2-year OS and RFS in patients with undetected methylation gene mutations were compared between the two groups. OS (P=0.007) and RFS (P=0.041) were significantly improved in the observation group compared with those in the control group (Figs. 6 and 7).

## Discussion

AML is a heterogenous malignant disease, and its pathogenesis remains elusive. Although the conventional chemotherapy regimen achieves a 60-80% CRR in adult patients, the remission time is short and the majority of the patients eventually

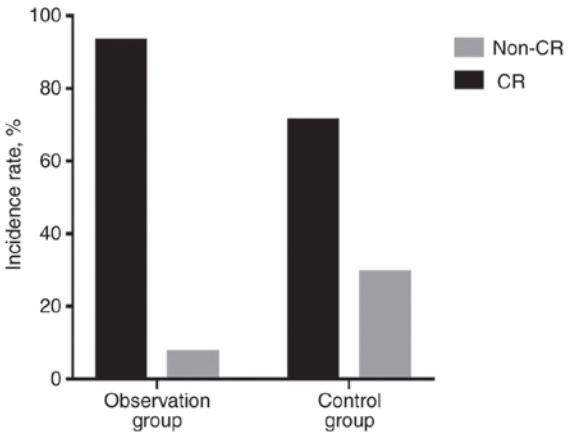


Figure 3. Comparison of CR in patients aged <60 years between the two groups. The y-axis represents the incidence rate. For patients aged <60 years, the observation group consisted of 26 patients with CR (92.9%) and the control group consisted of 32 patients with CR (71.1%). The non-CR rates were 7.1 and 28.9% for the observation and control groups, respectively. P<0.05. CR, complete remission.

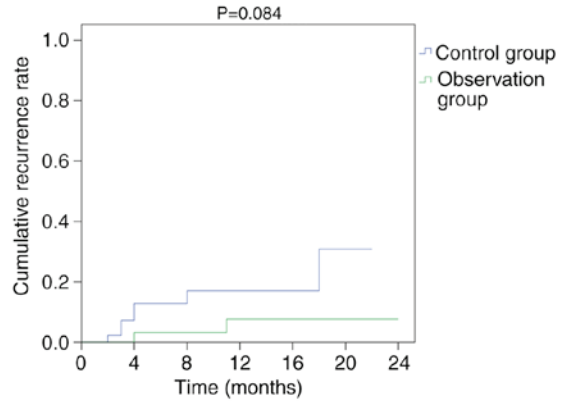


Figure 4. Recurrence curves for the two groups. The y-axis represents the cumulative recurrence rate. There was no significant difference in the cumulative recurrence rate between the two groups, as analyzed by the Kaplan-Meier method. P>0.05. Blue, control group; green, observation group.

develop disease relapse (4-6). Therefore, there is an urgent need to improve the remission rate and reduce the recurrence rate in patients with AML. Although recent studies have suggested that decitabine treatment can improve the remission rate of patients with AML (3,6,13), it has not been reported whether demethylation drugs are beneficial for reducing the recurrence rate of AML. In addition, patients with AML with methylation gene mutations (including DNMT3A and TET2) have a poor prognosis (8); however, certain patients with AML may have undetected methylation gene mutations. It has not been reported whether or not decitabine is beneficial for the treatment of these cases and for patients with AML without methylation gene mutations.

With the rapid development of epigenetics, the role of DNA methylation abnormalities in the occurrence and transformation of neoplasms has gradually been recognized (11,12). Previous studies have reported that high levels of DNA methylation are present in the genome of patients with AML, which can decrease the transcription of or completely silence genes related to reducing cell self-monitoring, and

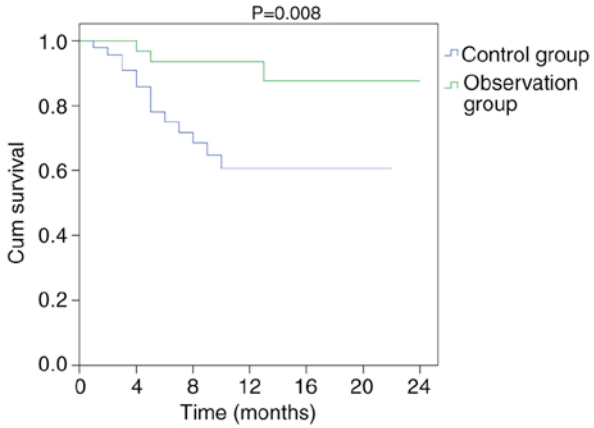


Figure 5. OS curves for the two groups. The y-axis represents the overall survival rate. There was a statistically significant difference in OS between the two groups, as analyzed by the Kaplan-Meier method. P<0.05. Blue, control group; green, observation group. OS, overall survival.

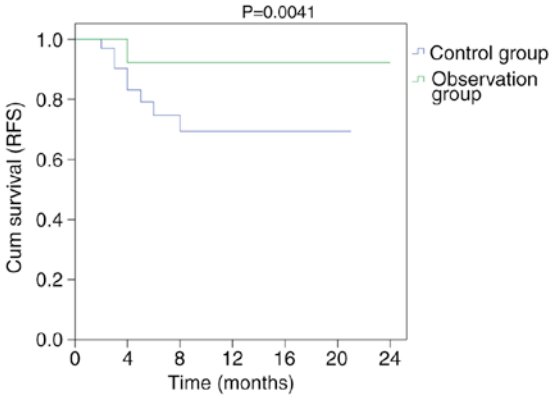


Figure 7. Comparison of RFS in patients with undetected methylation gene mutations between the two groups. The y-axis represents the RFS rate. Statistically significant differences in patients with undetected methylation gene mutations between the two groups were identified, as analyzed by the Kaplan-Meier method. The median RFS time was 12 and 9 months for the observation and control groups, respectively. P<0.05. Blue, control group; green, observation group. RFS, recurrence-free survival.

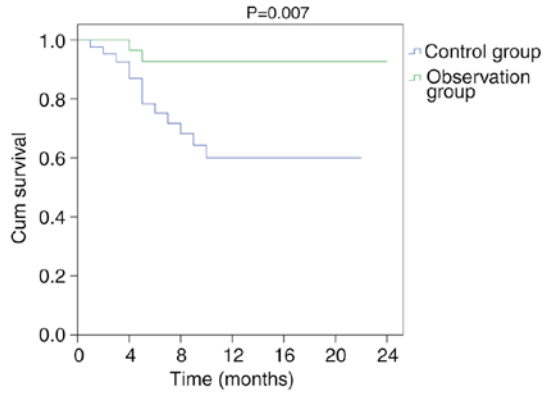


Figure 6. OS curves for patients with undetected methylation gene mutations in the two groups. The y-axis represents the OS rate. Statistically significant differences in patients with undetected methylation gene mutations between the two groups were identified, as analyzed by the Kaplan-Meier method. P<0.05. Blue, control group; green, observation group. OS, overall survival.

inhibiting abnormal differentiation and proliferation (10,11). Gene promoter-specific hypermethylation contributes to tumor development during AML (10,11); therefore, the use of demethylation drugs, which can reverse the hypermethylation status, may serve as a promising strategy for treating leukemia and reducing the risk of recurrence.

The demethylating drug decitabine was originally approved for the treatment of MDS, and was later approved for the first-line treatment of AML patients aged >65 years (19). Several studies have reported that decitabine improves the efficacy of treatment for AML (3,6); however, the majority of studies have focused on elderly patients with AML and administrated decitabine as a monotherapy, low-dose chemotherapy, or combined with A or aclarubicin (C) + A + granulocyte colony-stimulating factor (G) regimen (6,13). The present study compared the efficacy of D + A, I + A and H + A modalities with or without decitabine, analyzing the efficacy of decitabine in the treatment of newly diagnosed non-elderly AML. A total of 81 patients were enrolled, with 35 patients in the observation group and 46 patients in the control group. The median age of the enrolled patients was 58.5 years, and there was no significant difference in age between the two groups. In the control group, the CRR was 69.6% and the ORR was 84.8%, which was consistent with the literature (4-6). Furthermore, the CRR and ORR of the induction regimen with decitabine were significantly higher compared with those in the control group (P=0.017 and P=0.044, respectively). In addition, it has been reported that the '7+3' conventional chemotherapy modality has a CRR of 60-85% in patients with AML aged <60 years (20,21). In the present study, 73 patients aged <60 years were examined. The CRR in patients <60 years was increased in the observation group (92.9%) compared with the control group (71.1%; P=0.025). The results suggested that, when combined with the conventional induction therapy used for AML, decitabine significantly improves the CRR and ORR of patients, and it plays a particularly important role in the treatment of non-elderly patients with AML.

Welch *et al* (18) recruited 116 patients with AML/MDS who were treated with decitabine monotherapy, identifying a higher response rate in patients with an unfavorable-risk cytogenetic profile (67%; P<0.001). Bai *et al* (19) compared the curative effect of the C + A + G regimen with that of the C + A + G regimen combined with decitabine in elderly patients with AML, reporting that the CRR and ORR of patients receiving the C + A + G regimen combined with decitabine were increased compared with those in the C + A + G group (57.1 vs. 15% and 71.4 vs. 25%, respectively; P<0.05). Although the number of favorable-risk patients was not sufficient to perform statistical analyses in the present study, the observation group displayed a higher CRR (90.3 vs. 67.5%) in intermediate- and unfavorable-risk patients compared with the control group (P=0.022).

Additionally, a number of studies have reported that decitabine has been effective in the treatment of AML with DNA methylation gene mutations. A study investigating the use of decitabine alone or in combination with bortezomib indicated that the CRR and OS were increased in patients with AML with DNMT3A mutations compared with patients with AML with wild-type DNMT3A (22). Certain

patients with AML displayed undetected methylation gene mutations; therefore, whether individuals with undetected methylation gene mutations benefited from the administration of decitabine has not been reported. Whole-genome hypermethylation is widespread in AML and is associated with poor clinical outcome (10); therefore, the majority of AML cases with undetected methylation gene mutations display a low frequency of DNA methylation (10,12). DNA methylation is reversible; therefore, it was hypothesized that demethylating drugs may reduce the frequency of methylation to reduce the occurrence and recurrence of AML, and improve treatment efficacy. The CRR of patients with undetected methylation mutation genes was increased in the observation group compared with that in the control group (P=0.028), which was consistent with this hypothesis.

In addition, a comparison of the survival analysis of the two groups was performed. The recurrence rate in the observation group was reduced compared with that in the control group (5.7 vs. 15.2%, respectively; P>0.05); however, this decrease was not statistically significant. If the follow-up period was prolonged, significant differences may have been observed. Furthermore, the 2-year OS in the two groups was assessed. The results indicated that induction therapy with decitabine significantly prolonged the 2-year OS of patients with AML compared with induction therapy without decitabine (P=0.008). In 2012, a phase III clinical trial of decitabine monotherapy with A or supportive therapy in elderly patients with AML was conducted (23). The results indicated that the decitabine monotherapy group displayed an improved CR; although the OS was not significantly different, the difference exhibited a trend in favor of decitabine (24,25).

In the present study, the differences in the 2-year OS and RFS between the two groups in patients with undetected methylation gene mutations were statistically significant (P=0.007 and P=0.041, respectively). The results further supported the hypothesis that decitabine may improve the efficacy of AML treatment strategies and reduce recurrence. However, the present study had a number of limitations, including a small sample size, limited follow-up and the lack of a prospective study; therefore, large-scale and prospective clinical trials are required to verify the results of the present study.

The combination of decitabine and D + A, I + A or H + A regimens as induction chemotherapy displayed improved induction responses, reduced recurrence and prolonged survival in patients with *de novo* non-elderly AML (non-M3). Additionally, OS and RFS were prolonged in patients with undetected methylation gene mutations.

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**Availability of data and materials**

All data generated or analyzed during the present study are included in the published article.

**Authors' contributions**

DZ, LZ and LH conceived and designed the study. LZ, DZ, LH, YH, LH, YL, ZS, JW, ZW, XM, YW and MX collected and analyzed the data. LZ, DZ and YL wrote the manuscript. All authors were responsible for data collection and analysis, and read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The present study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval no. TJ-IRB20190913). Patient consent was not obtained, as the Ethics Committee approved the application for exemption of informed consent.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Siegel R, Ma J, Zou Z and Jemal A: Cancer statistics, 2014. CA Cancer J Clin 64: 9-29, 2014.
2. Juliusson G, Lazarevic V, Hörstedt AS, Hagberg O and Höglund M; Swedish Acute Leukemia Registry Group: Acute myeloid leukemia in the real world: Why population-based registries are needed. Blood 119: 3890-3899, 2012.
3. Li WY, Wang Y, Chen SN, Qiu HY, Fu ZZ, Wu DP and Sun AN: Consolidation therapy with decitabine and intermediate-dose cytarabine followed by HLA-mismatched peripheral blood stem cells infusion for older patients with acute myeloid leukemia in first remission. Leuk Lymphoma 59: 1652-1658, 2018.
4. Thol F, Schlenk RF, Heuser M and Ganser A: How I treat refractory and early relapsed acute myeloid leukemia. Blood 126: 319-327, 2015.
5. Sasine JP and Schiller GJ: Emerging strategies for high-risk and relapsed/refractory acute myeloid leukemia: Novel agents and approaches currently in clinical trials. Blood Rev 29: 1-9, 2015.
6. Li G, Ren L, Li G, *et al*: The effectiveness comparison between the CLAG regimens and MEA regimens for the treatment of patients with relapsed or refractory acute myeloid leukemia. J Mod Oncol 26: 264-268, 2018 (In Chinese)
7. Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC and Majeti R: Preleukemic mutations in human acute myeloid leukemia affect epigenetic regulators and persist in remission. Proc Natl Acad Sci USA 111: 2548-2553, 2014.
8. Tan Y, Liu H and Chen S: Mutant DNA methylation regulators endow hematopoietic stem cells with the preleukemic stem cell property, a requisite of leukemia initiation and relapse. Front Med 9: 412-420, 2015.
9. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M and Vardiman JW: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127: 2391-2405, 2016.
10. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR and Sultan C: Proposals for the classification of the acute leukemias. French-American-British (FAB) co-operative group. Br J Haematol 33: 451-458, 1976.
11. NCCN, Acute Myeloid Leukemia, NCCN Clinical Practice Guidelines in Oncology. Accessed April 4, 2016.
12. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, *et al*: Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129: 424-447, 2017.

13. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, Schiffer CA, Doehner H, Tallman MS, Lister TA, *et al*: Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 21: 4642-4649, 2003.
14. Spencer DH, Russler-Germain DA, Ketkar S, Helton NM, Lamprecht TL, Fulton RS, Fronick CC, O'Laughlin M, Heath SE, Shinawi M, *et al*: CpG island hypermethylation mediated by DNMT3A is a consequence of AML progression. Cell 168: 801-816.e13, 2017.
15. Deneberg S, Grövdal M, Karimi M, Jansson M, Nahi H, Corbacioglu A, Gaidzik V, Döhner K, Paul C, Ekström TJ, *et al*: Gene-specific and global methylation patterns predict outcome in patients with acute myeloid leukemia. Leukemia 24: 932-941, 2010.
16. Döhner H, Weisdorf DJ and Bloomfield CD: Acute myeloid leukemia. N Engl J Med 373: 1136-1152, 2015.
17. Short NJ, Rytting ME and Cortes JE: Acute myeloid leukaemia. Lancet 392: 593-606, 2018.
18. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, Wilson RK, Baty JD, Duncavage EJ, Tandon B, *et al*: TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med 375: 2023-2036, 2016.
19. Bai X, Xiao X, Li Y, Zhao M and Deng Qi: Curative effect of CAG regimen compared with CAG combined with decitabine regimen in elderly patients with acute myeloid leukemia. Clin Focus 33: 240-243, 2018 (In Chinese).
20. Metzeler KH, Walker A, Geyer S, Garzon R, Klisovic RB, Bloomfield CD, Blum W and Marcucci G: DNMT3A mutations and response to the hypomethylating agent decitabine in acute myeloid leukemia. Leukemia 26: 1106-1107, 2012.
21. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, Gau JP, Chou WC, Buckstein R, Cermak J, *et al*: Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 30: 2670-2677, 2012.
22. Thomas XG, Arthur C, Delaunay J, Jones M, Berrak K and Kantarjian HM: A post hoc sensitivity analysis of survival probabilities in a multinational phase III trial of decitabine in older patients with newly diagnosed acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 14: 68-72, 2014.
23. Nieto M, Demolis P, Béhanzin E, Moreau A, Hudson I, Flores B, Stemplewski H, Salmonson T, Gisselbrecht C, Bowen D and Pignatti F: The European medicines agency review of decitabine (Dacogen) for the treatment of adult patients with acute myeloid leukemia: Summary of the scientific assessment of the committee for medicinal products for human use. Oncologist 21: 692-700, 2016.
24. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, Li Y, Bhagwat N, Vasanthakumar A, Fernandez HF, *et al*: Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 18: 553-567, 2010.
25. Rothenberg-Thurley M, Amler S, Goerlich D, Köhnke T, Konstandin NP, Schneider S, Sauerland MC, Herold T, Hubmann M, Ksienzyk B, *et al*: Persistence of pre-leukemic clones during first remission and risk of relapse in acute myeloid leukemia. Leukemia 32: 1598-1608, 2018.