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Original Article

Chidamide and Decitabine in Combination with a HAG Priming Regimen for Acute Myeloid Leukemia with *TP53* Mutation

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We analyzed the treatment effects of chidamide and decitabine in combination with a HAG (homoharringtonine, cytarabine, G-CSF) priming regimen (CDHAG) in acute myeloid leukemia (AML) patients with *TP53* mutation. Seven *TP53* mutated AML patients were treated with CDHAG. The treatment effects were assessed using hemogram detection and bone marrow aspirate. The possible side effects were evaluated based on both hematological and non-hematological toxicity. Four of the seven patients were classified as having achieved complete remission after CDHAG treatment; one patient was considered to have achieved partial remission, and the remaining two patients were considered in non-remission. The overall response rate (ORR) to CDHAG was 71.4%. Regarding the side effects, the hematological toxicity level of the seven patients ranged from level III to level IV, and infections that occurred at lung, blood, and skin were recorded. Nausea, vomiting, liver injury, and kidney injury were also detected. However, all side effects were attenuated by proper management. The CDHAG regimen clearly improved the ORR (71.4%) of *TP53*-mutated AML patients, with no severe side effects.

Key words: acute myeloid leukemia, chidamide, decitabine, HAG, *TP53* mutation

Acute myeloid leukemia (AML) is a heterogeneous aggressive malignancy that is characterized by the proliferation and accumulation of myeloid blast cells in the bone marrow [1]. It is the most common type of acute leukemia in adults, and it has an annual incidence of 0.0035% for populations ≤ 60 years old and an annual incidence of 0.002% for those ≥ 60 years old [2]. Although emerging treatment strategies have been developed for AML, the 5-year-survival rate of the patients is around 40-45% in patients ≤ 65 years of age, and it decreases to as low as 20% for patients ≥ 65 years old [3, 4]. The low cure rate and high relapse rate of AML are attributed to the strong chemoresistance of the disease [1], which presents a major burden for the treatment of AML patients. It is commonly recognized that genetic mutations in AML predict the risk of AML resistance or recurrence. With the help of the advanced sequencing technologies, an increasing number of pathogenic alterations involved in the progression of AML has been identified [3, 5-7]. Some of the mutational aberrations are confirmed to play an important role in the initiation of AML [8].

Tumor protein p53 (*TP53*) is a well-characterized pro-tumor gene that encodes p53 protein, which is critical to the regulation of cellular stress response [9, 10]. Although *TP53* mutation only occurs in < 10% of patients with de novo AML, it is an adverse risk factor that is strongly associated with resistance to chemotherapy [5, 11, 12]. Chemoresistance results in an

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extremely high relapse rate and a worse survival rate in AML patients [13-16]. The issue of how to effectively manage AML patients with *TP53* mutation is a pressing issue in the field of leukemia treatment. Hypomethylating drugs have shown to be effective for high-risk AML patients and were used to treat *TP53* mutated patients in a few studies [17]. Moreover, histone deacetylase (HDAC) inhibitors (HDACis) have shown a promising potential to induce cell death by activating multiple cell-signaling pathways in AML cell lines in preclinical experiments [18, 19].

Although it has been difficult to transfer the beneficial effects of HDACis to clinical success, it was recently shown that the combined use of a hypomethylating drug (decitabine) and an HDACi (chidamide) resulted in synergistic effects for the inhibition of cell proliferation and the induction of apoptosis of human myeloid leukemia cell lines [20]. Chidamide possesses significant single-agent activity and showed manageable toxicity in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma [21], and its activity might enhance the treatment effects of decitabine. We thus hypothesized that the combined use of decitabine and chidamide might be an effective treatment strategy for *TP53*-mutated AML.

To test this hypothesis, we performed the present retrospective study with the treatment information of seven AML patients with *TP53* mutation. The patients were all treated with the combined administration of decitabine and chidamide along with the conventional priming HAG regimen (CDHAG). HAG therapy contains homoharringtonine (HHT), cytarabine (Ara-C), and granulocyte-colony stimulating factor (G-CSF). Homoharringtonine (HHT) is an alkaloid isolated from China's unique plant *Torreya grandis*, and it is a highly effective antitumor drug that was successfully developed in China. It has been demonstrated in clinical studies that HHT has a beneficial effect on AML, acute monocytic leukemia, erythroid leukemia and other acute non-lymphatic leukemias, and chronic myeloid leukemia.

We collected and analyzed the data of the seven patients' baseline information, relapse time, and treatment results to determine the effects of the above-described combined therapy. The results of our analyses comprise valuable information for the clinical management of *TP53*-mutated AML.

Patients and Methods

Patients. We collected the clinicopathological information of seven AML patients with *TP53* mutation from clinical trial no. ChiCTR1800020372. The patients were admitted to the Department of Hematology in the People's Hospital of Jiaozuo City, China during the period from December 2016 to May 2020. All patients were diagnosed as having *TP53*-mutated AML based on the results of bone marrow cell morphology, cellular immunology, cytogenetics, and molecular biology in accord with the MCIM (morphology + immunology + cytogenetics + molecular) criteria [22]. The details of the MCIM criteria and directions for the evaluations are as follows.

(1) Cell morphology diagnosis

Bone marrow punctures and smears were performed according to conventional methods. Some of the smears were stained with Wright's, and the other smears were stained with peroxidase enzyme staining (POX), glycogen staining (PAS), and naphthol esterase (NAE). Two hundred cells were counted under the oil glass and classified according to the FAB (French-American-British) classification method.

(2) Cellular immunophenotyping

Take 1-2 mL of the patient's bone marrow to detect leukemia cell antigen. The interpretation of immunophenotyping results refers to the diagnostic standards used in China and the antigen score standards advocated by European countries and the U.S.

(3) Chromosome karyotype analysis

Collect 3-4 mL of bone marrow specimen and use heparin for anticoagulation. Separate mononuclear cells and culture for 24 h. Routinely prepare chromosome specimens; use G-banding technology to band and analyze 20 nuclear cleavage phases under the microscope. A chromosome karyotype analysis was performed according to International System for Human Cytogenetic Nomenclature (ISCN).

(4) Fusion gene detection

Take 2 mL of the patient's EDTA-anticoagulated bone marrow and use reverse transcription-polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH) to detect fusion genes such as AML1/ETO fusion gene and gene mutations such as *TP53*.

Of the seven patients examined herein, those with relapse AML were diagnosed based on the following criteria: the detection of leukemia cells in peripheral

blood or anarchaeocyte proportion in bone marrow > 5%, or the detection of an infiltration of leukemia cells in extramedullary regions after complete remission (CR).

The criteria used to diagnose refractory AML were as follows: failure to respond to treatment with standard therapies for two courses; relapse of AML within 12 months after a CR; two or more relapses episodes; consistent existence of extramedullary leukemia cells [23]. All of the patients examined in this study provided written informed consent for the use of their historical information. The study was approved by the ethics committee of Jiaozuo People's Hospital (approval no. MEC-2018-10-28) and complied with the the provisions of the Declaration of Helsinki.

Treatment strategy. All 7 patients were treated with CDHAG as follows. The chart below explains the CDHAG regimen that was used. (As shown in Table 1)

- Chidamide 30 mg, oral administration, biw (*i.e.*, 2×/week), day (d)1-d11
- Decitabine 25 mg injection, qd (*i.e.*, 1×/day) and ivgtt (intravenous drip), d1-d5
- Cytarabine 15 mg/m^2 injection, q12h (*i.e.*, 1×/every 12 h) and iH (subcutaneous injection), d3-d9
- Homoharringtonine 2 mg injection, qd and ivgtt, d3-d9
- Recombinant human granulocyte colony stimulating factor (rhG-CSF) 300 μg injection, qd, iH, d1-d9
- White blood cell (WBC) count $< 10 \times 10^9$/L on d0-d9, WBC count $\geq 10 \times 10^9$/L on d1-d9 shoule be met.

The morphology of each patient's bone marrow was examined on the 10th day of the treatment. The injections of decitabine, cytarabine, homoharringtonine, and filgrastim were extended if the blast proportion was > 20% or the decreased proportion was < 50%.

Treatment effectiveness assessment. Treatment effectiveness was assessed 3-4 weeks after the end of the therapy regimen, and the patients' responses were classified into complete remission (CR), partial remission (PR), and non-remission (NR) based on the published criteria [23]. Complete remission (CR): bone marrow (BM) < 5% blasts in an aspirate with spicules; ≥ 200 cells must be enumerated; no blasts with Auer rods or persistence of extramedullary disease; absolute neutrophil count > 1,000/μL (blasts < 5%); platelets ≥ 100,000/μL (blast < 5%). Partial remission (PR): decrease of ≥ 250% in the percentage of blasts to 5-25% in the BM aspirate and the normalization of blood counts, as noted above. Non-remission (NR): failure to attain a CR or PR following exposure to at least two courses of intensive induction therapy. The overall response rate (ORR) was calculated as the ratio of (number of CRs + PRs/the total number of patients) × 100%.

Safety assessment. The safety of the treatment strategy was assessed based on both hematological toxicity and non-hematological toxicity. The determination of hematological toxicity included the detection of the numbers of leukocytes, red blood cells, and platelets. The evaluation of non-hematological toxicity included the records of infections, nausea, vomiting, and assessments of liver and kidney functions. The

Table 1 The CDHAG regimen

Day	Chidamide	Decitabine	Ara-C	HHT	rhG-CSF
1	30 mg, po	25 mg, ivgtt			300 μg, iH
2		25 mg, ivgtt			300 μg, iH
3		25 mg, ivgtt	15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
4	30 mg, po	25 mg, ivgtt	15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
5		25 mg, ivgtt	15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
6			15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
7			15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
8	30 mg, po		15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
9			15 mg/m^2, q12h, iH	2 mg, ivgtt	300 μg, iH
10					
11	30 mg, Po				

Ara-C, cytarabine; HHT, homoharringtonine; ivgtt, intravenous drip; iH, subcutaneous injection; po, per os (orally); q12h, every 12 hours; rhG-CSF, recombinant human granulocyte colony stimulating factor.

overall safety of the treatment strategy was summarized based on the World Health Organization (WHO) classification criteria for adverse drug reactions and the WHO classification criteria for acute and subacute chemotherapeutic drugs.

Statistical analysis. The data were tested using the Shapiro-Wilk test to determine whether they had a normal distribution and then applied to a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests, with Prism (ver. 8.2.1; GraphPad Software, La Jolla, CA, USA). Data are expressed as the mean ± S.D. Statistical significance was accepted at p-values < 0.05.

Ethical approval. The study was a retrospective analysis, and we used data from hospital records. Informed Consent: All patients signed written informed consent forms before the start of the regimens.

Results

Baseline information. As shown in Table 2, there were four males and three females, three relapse AML cases, three refractory AML cases, and one initial treatment AML patients. The information regarding FAB type, molecular detection, and karyotype of the patients is also provided in Table 2. The conventional chemotherapies and the relapse times of the patients are shown in Table 3.

Treatment results. After the treatment regimen with CDHAG, four of the seven patients achieved a CR, one patient attained a PR, and the remaining two patients were identified as NR (Table 4). The ORR of the treatment strategy was 71.4%. The details of the individual patients is as follows (Table 4).

Patient No. 1 was diagnosed as having refractory AML upon admission. After one course CDHAG treatment, the *TP53* mutation was absent and the karyotype was restored. The patient then received another five courses of CDHAG treatment to consolidate the desired therapeutic effects. The immunological relapse of Patient No. 1 was recorded 12 months after the treatment, and hematologic relapse was recorded 14 months after the treatment. The patient died 18 months after the CDHAG treatment.

Patient No. 2 and Patient No. 3 were diagnosed as refractory AML cases, and the CDHAG treatments had no significant therapeutic effects on either patient. They died after one treatment course due to multiple organ failure.

Patient No. 4 was diagnosed as a relapse AML case, and the *TP53* mutation was identified at the third relapse. After one course of CDHAG treatment, TP53 mutation was restored. The patient then received three more courses of CDHAG treatment and a long-term administration of interferon (IFN), interleukin (IL)-2, and thalidomide to consolidate the desired therapeutic effects.

Patient No. 5 was diagnosed as a relapse AML case.

Table 2 Baseline clinicopathological information

No.	Gender	Age (Years)	AML type	FAB	Molecular biological characteristics	Karyotype
1	Female	63	Refractory	M2	TP53, NPM1, KMT2D, CREBBP	44−48, XX, −X, del(1)(q12), −5, del6(q22), del8(p12), −9, −13, der(17), +21, +mar, inc[cp10]
2	Male	26	Refractory	M5	TP53, NRAS, ABCB1, IKZF1	48, XY, +i(10)(q10), t(11 ; 19)(q23 ; p13), +13[20]
3	Female	71	Refractory	M5	TP53, ASXL1, KRAS	46, X, −X, der(3), +der(4), der(5), der(7)(p14), −8, del(19)(q13), der(10), +12, del(12), −15, −16, +mar2, inc[cp10]
4	Male	38	Relapse	M5	TP53, CEBPA single mutation	46, XY[20]
5	Female	53	Relapse	M5	TP53, TET2, GATA2, CEBPA single mutation	46, XX[20]
6	Male	52	Relapse	M4	TP53	46, XY[20]
7	Male	36	Initiation	M2	TP53, ABCB1	48−49, XY, +Y, del(5)(q13q31), +6, −7, +8, +9, t(11 ; 13)(q13q31), add(12)(p13), +der(13)t(11 ; 13)(q13q31), der(17), inc[cp10]

Table 3 Conventional therapies and relapse information of the patients

No.	Previous chemotherapy regimen	Relapse time	CR time after relapse (month)
1	DAC*1, DAC+Ren*3	0	NA
2	DA, DCAG, HAE, IA	0	NA
3	IA, DCAG	0	NA
4	DA, GHAA*2, MA, DCAG, DGAA, ID-Ara-c+Ida*2, DCAG	2	CR1 14, CR2 26
5	DA*2, DAC+MAC	1	9
6	IA*2, IHA, IA, MAC	1	5
7	NA	0	NA

DA, Daunorubicin, Cytosine arabinoside; IA, Idarubicin, Cytosine arabinoside; MA, Mitoxantrone, Cytosine arabinoside; ID-Ara-c+Ida, Intermediate-Dose Cytosine arabinoside, Idarubicin; DAC, Daunorubicin, Cytosine arabinoside, Cyclophosphamide; MAC, Mitoxantrone, Cytosine arabinoside, Cyclophosphamide; IHA, Idarubicin, Homobarringtonie, Cytosine arabinoside; HAE, Homobarringtonie, Cytosine arabinoside, Etoposide; DAC+Ren, Daunorubicin, Cytosine arabinoside, Cyclophosphamide, Lenalidomide; DCAG, Decitabine, Cytosine arabinoside, Aclacinomycin, Human granulocyte conlony stimulating factor; GHAA, Decitabine, Homobarringtonie, Cytosine arabinoside, Aclacinomycin.

Table 4 Treatment effectiveness assessment results

No	Peripheral blood					Bone marrow		effec-tiveness	OS (month)
	WBC ($\times 10^9$/L) (before/after)	HB (g/L) (before/after)	PLT (10×10^9/L) (before/after)	Archaeocyte (before/after)	Morphology (before/after)	Immune residual (before/after)	TP53 mutation frequency (before/after)		
1	1.1/3.9	94/117	2/113	7%/0	42%/2%	13.2%/0	15.0%/0	CR	18
2	88.1/9.3	71/89	9/107	98%/0	96%/98%	87.31%/81.6%	23.0%/23.2%	NR	Death
3	3.0/5.6	86/98	376/128	9%/0	26%/21%	12.5%/11.0%	45.10%/43.8%	NR	Death
4	3.6/4.8	161/104	174/218	0/0	16.5%/1.0%	18.31%/0	10.2%/0	CR	16
5	2.2/3.5	94/102	23/117	14%/0	19.5%/0	17.72%/0	30.5%/23.7%	CR	Death
6	16.8/8.7	67/128	27/142	9%/0	25%/5%	12.66%/0.9%	18.70%/14.3%	PR	3
7	6.0/5.8	49/108	3/118	14%/0	22.5%/0	17.87%/0	25.3%/22.1%	CR	5

Complete remission (CR): BM<5% blasts in an aspirate with spicules; at least 200 cells must be enumerated; no blasts with Auer rods or persistence of extramedullary disease; absolute neutorphil count>1000/mcl (blast<5%); platelets≥100000/mcl (blast<5%).
Partial remission (PR): decrease of at least 50% in the percentage of blasts to 5% to 25% in the BM aspirate and the normalization of blood counts, as noted above.
non-remission (NR): failure to attain CR or PR following exposure to at least 2 courses of intensive induction therapy.

One course of CDHAG treatment led to a CR, but the treatment had no influence on the mutation state of *TP53*. After another course of CDHAG to restore the *TP53* mutation, the patient's AML symptoms relapsed again and led to her death 5 months after the first treatment.

Patient No. 6 was diagnosed as a relapse AML case and received one course of the CDHAG treatment, which led to a PR. The patient then received one course of treatment with chidamide+azacitidine+homoharringtonine+G-CSF, and one course of treatment of with venetoclax+homoharringtonine+etoposide, which resulted in little improvement of the prognosis. Long-term treatment with IFN, IL-2, and thalidomide was administered until the patient was lost to follow-up.

Patient No. 7 was an initial-treatment case with *TP53* mutation. After one course of the CDHAG regimen, the patient achieved a CR with restorations of the *TP53* mutation and karyotype. The patient continued to receive long-term CDHAG treatment before undergoing an allogeneic hematopoietic stem cell transplantation.

Safety assessment. We assessed the safety of the CDHAG strategy based on the WHO classification criteria for adverse drug reactions given and the WHO classification criteria for acute and subacute chemotherapeutic drugs. The hematological toxicity levels of the seven patients were III-IV. The patients thus received additional treatments with filgrastim, recombinant human thrombopoietin, suspension red blood cells, and platelets to attenuate the hematological toxicity associated with the CDHAG regimen. Regarding the

Table 5 Safety assessment

No	Myelosuppression	Infection	Nausea	Liver injury	Kidney injury
1	Ⅳ	Lung	Ⅱ	0	0
2	Ⅳ	Lung	Ⅱ	0	Ⅱ
3	Ⅳ	Blood, lung	Ⅱ	Ⅰ	Ⅱ
4	Ⅲ	Blood, face	Ⅰ	0	0
5	Ⅲ	Lung, skin	Ⅱ	Ⅱ	0
6	Ⅳ	Lung	Ⅰ	0	0
7	Ⅳ	Lung	Ⅰ	0	0

non-hematological toxicity assessment, 6 of the 7 patients developed lung infections, two developed blood infections, and two experienced skin infections (Table 5). All of these infections were alleviated by anti-infection therapies. Other non-hematological toxicities associated with CDHAG treatment included nausea, vomiting, liver injury, and kidney injury, which could be attenuated by proper treatments. The detailed information about the side effects associated with CDHAG therapy is provided in Table 5.

Discussion

As an independent factor influencing the prognosis of AML, *TP53* mutation contributes to the low recovery rate, high relapse rate, and short survival duration of AML patients, which makes the clinical management of patients *TP53*-mutated AML a challenge. In a previous investigation, the median survival time of *TP53*-mutation AML patients (14.1 months) was significantly shorter than that of AML patients without *TP53* mutation (31.4 months) [24]. The identification of effective management strategies for *TP53*-mutated AML is thus an urgent task in the field of AML.

We analyzed the treatment results of seven *TP53*-mutation AML patients treated with CDHAG, and the results demonstrated that after different courses of CDHAG treatments, most of the patients showed improvement in their conditions. The ORR of CDHAG treatment was 71.4%, indicating the overall attenuating effects of CDHAG on *TP53*-mutated AML.

Decitabine is a hypomethylating drug that is widely used for the treatment of diverse malignant hematopoietic diseases [25,26]. It is reported that decitabine can increase AML cells' sensitivity to cytarabine, which subsequently strengthens the anti-AML effects of toxic lymphocytes and induces the apoptosis of AML cells by activating the TRAIL pathway [27]. Welch *et al.* reported that patients with malignant myeloid cancer and *TP53* mutation showed high sensitivity to decitabine treatment [28]. A study by Chang *et al.* revealed that decitabine treatment significantly increased the CR rate of patients with myelodysplastic syndrome (MDS) and *TP53* mutation to 66.7% [29]. The combined use of decitabine and CAG (cytarabine [C], aclarubicin [A], and granulocyte colony-stimulating factor [G]) substantially increased the median survival time of *TP53*-mutation AML patients to 30.0 months [24]. The administration of decitabine was shown to rapidly eliminate *TP53* mutation in AML patients, further confirming the treatment potential of hypomethylating drugs against *TP53*-mutated AML [24].

Chidamide is an HDACi drug that was initially used for the treatment of peripheral T-cell lymphoma. HDACis also exhibited potential effectiveness against AML cell lines in both pre-clinical and clinical experiments via multi-pronged mechanisms [18,19]. For example, chidamide treatment inhibited the malignant hyperplasia of AML and MDS cells by modulating the SOCS3/JAK2/STAT3 axis [30,31]. Moreover, the co-administration of chidamide with conventional therapies has led to the alleviation of AML and MDS symptoms [32,33].

Based on the current data, it is clear that the combined application of decitabine and chidamide not only had powerful beneficial effects on AML symptoms but also restored the mutation of *TP53* in AML patients. Not only using the treatment with the combination of decitabine and chidamide, this study also employed HAG priming regimen to increase the treatment success. The HAG method was developed from the CAG method, which has been widely used for the treatment of refractory/relapse AML since 1995 and has achieved considerable effectiveness [34].

Our present study analyzed the treatment results of the CDHAG strategy against *TP53*-mutated AML. The results demonstrate that this treatment clearly improved the ORR (71.4%). Moreover, no severe side effects were observed during the treatments, indicating the promising potential of using CDHAG against *TP53*-mutated AML. However, the sample size of the current analysis was small (n = 7), and comprehensive analyses of other physiological parameters were lacking. To further test the application of the CDHAG strategy, investigations with larger sample sizes are needed.

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