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The therapeutic effect of decitabine combined with HAG in acute myeloid leukemia: a retrospective case-control analysis

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Abstract. – OBJECTIVE: Explore the efficacy of decitabine combined with homoharringtonine + cytarabine + granulocyte colony-stimulating factor (HAG) in the treatment of acute myeloid leukemia (AML).

PATIENTS AND METHODS: A retrospective analysis of clinical data of 125 patients with AML was done. Of them, 61 patients received a simple HAG treatment (HAG group), and 64 received decitabine combined with an HAG regimen (combined group). Treatment efficacy, immune function before and after the treatment, levels of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and incidence of adverse reactions in the two groups were compared.

RESULTS: The total response rate of the combined group (84.38%) was higher than that of the HAG group (65.63%) ($p < 0.05$). After the treatment, levels of CD4+ and CD4+/CD8+ in both groups increased and were significantly higher in the combined group compared to the HAG group. Levels of CD8+, bFGF and VEGF decreased compared to pre-treatment levels and were significantly lower in the combined group than in the HAG group ($p < 0.05$). There was no significant difference in the rate of adverse reactions between the two groups ($p > 0.05$).

CONCLUSIONS: Compared to HAG treatment alone, the combination of decitabine and HAG in the treatment of AML is safe, can significantly improve the immune function of the patients, regulate bFGF and VEGF levels, and improve overall treatment efficacy.

Key Words:
Acute myeloid leukemia, HAG, Decitabine.

Introduction

Acute myeloid leukemia (AML) can lead to excessive proliferation of abnormal hematopoietic progenitors in the bone marrow, inhibit normal hematopoietic function, and may invade other organs of the body[1,2]. AML is characterized by a rapid onset and progression, high mortality rate, and is associated with a significant burden on patients, their families and the healthcare system[3,4]. Therefore, early implementation of safe and effective treatment for AML is of great significance.

At present, AML drugs mainly include anti-tumor alkaloids, molecular targeting drugs, and adrenal cortical hormones[5]. Among them, anti-tumor plant-based drugs include homoharringtonine, vinorelbine, etc.[5,6]. Homoharringtonine is an alkaloid extracted from plants in the family Tricuspidae. Modern pharmacological studies have confirmed that homoharringtonine has an effective inhibitory effect on the incorporation of 3H labeled asparagine into proteins[6,7]. The HAG regimen is commonly used in AML chemotherapy. While this treatment regimen can alleviate clinical symptoms to a certain extent, the overall effect is below clinical expected levels[7,8]. Decitabine, a pyrimidine nucleoside analog that inhibits DNA methyltransferases and reactivates silenced genes, is also routinely used in treating AML[9,10].

In recent years, our hospital has adopted a combined regimen of decitabine and HAG to treat patients with AML. This retrospective study

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aimed to explore the therapeutic effect of decitabine combined with HAG to provide a reference for the clinical treatment of AML

Patients and Methods

Medical records of 125 AML patients (64 males and 61 females), admitted to our hospital from January 2020 to December 2022, were retrospectively selected. The Ethics Committee of our hospital approved this study on May 23rd, 2023, No. NYL2022106. The age of the patients ranged from 24 to 71 years, with an average age of 44.30 ± 11.39 years. A total of 61 patients received HAG treatment and were assigned to the HAG group; 64 patients were treated with decitabine combined with HAG and were assigned to the combined group.

Inclusion Criteria

- Meets AML diagnostic criteria[10].
- Initial diagnosis.
- Complete medical record information.
- Age ≥ 18 years old.

Exclusion Criteria

- Other hematological diseases or malignant tumors.
- Allergic constitution and allergies to research drugs.
- Organic lesions in vital organs.
- Contraindications to radiotherapy and chemotherapy.
- Mental illness.
- Cardiovascular and cerebrovascular diseases.
- Breastfeeding and pregnant women.

HAG Protocol

Intravenous infusion of homoharringtonine (Hangzhou Minsheng Pharmaceutical Co., Ltd.; Approval No.: H33020007) 1 mg/m^2/day from day 1 to day 8; subcutaneous injection of cytarabine [Atvis (Foshan) Pharmaceutical Co., Ltd.; Approval No.: JX20040073] 10 mg/m^2/12 hours on days 1 to 14; subcutaneous injection of granulocyte colony-stimulating factor (Qilu Pharmaceutical Co., Ltd.; Approval No.: S19990050) 200 μg/m^2/d on days 1 to 14.

Dicitabine Regimen

Dicitabine (Zhengda Tianqing Pharmaceutical Group Co., Ltd.; Approval No.: H20120067) 15 mg/m^2 by intravenous drip was given on days 1 to 5, once a day.

Observation Indicators

1) Therapeutic effects. Complete remission - no extramedullary infiltration and Auer bodies, normal megakaryocytes and red blood cells, ≤ 5% of original granulocytes in bone marrow, no leukemia cells found on bone marrow examination, platelet count ≥ 100×10^9/L, neutrophil count ≥ 1.5×10^9/L, symptoms such as hepatosplenomegaly, bleeding, infection, and fever disappear; partial remission - 5% to 20% of primitive granulocytes in the bone marrow, with a neutrophil count of ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, clinical symptoms improved; failure to meet the above criteria is considered unrelieved; complete and partial remission are included in the total remission rate.

2) Immune function: blood levels of CD4+, CD8+, CD4+/CD8+, measured by flow cytometry (Beckman Kurt Company, CA, USA).

3) Serum levels of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) were measured using enzyme-linked immunosorbent assay. The reagent kit was purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd (Shanghai, China).

4) The incidence of adverse reactions, including fever, infection, liver dysfunction, gastrointestinal reactions, etc.

Statistical Analysis

All data analysis was conducted using SPSS 25.0 software (IBM Corp., Armonk, NY, USA). The normality of the data was evaluated using the Shapiro-Wilk test. The data of normal distribution was represented by mean ± standard deviation, independent sample *t*-test was used for inter-group comparison, and paired *t*-test was used for intra-group comparison before and after the treatment. The data with non-normal distribution was represented by median and interquartile intervals. Mann-Whitney U test was used for inter-group comparison, and Wilcoxon signed-rank test was used for intra-group comparison before and after the treatment. The counting data were represented by the number of use cases using Chi-square test. $p < 0.05$ indicated a statistically significant difference.

Results

A total of 125 AML patients were included in this study: 64 in the combined group and 61 in

Table I. Comparison of baseline data between two groups.

Group	n	Gender (male/female)	Age (years)	BMI (kg/m²)	FAB classification			
					M2	M4	M5	M6
Combined group	64	35/29	43.30±10.24	24.01±2.83	12 (18.75)	5 (7.81)	37 (57.81)	10 (15.63)
HAG group	61	29/32	45.34±12.47	24.38±2.87	11 (18.03)	8 (13.11)	30 (49.18)	12 (19.67)
χ^2/t		0.638	-1.000	-0.724	1.578			
p		0.424	0.319	0.470	0.664			

FAB = French–American–British; HAG = homoharringtonine + cytarabine + granulocyte colony-stimulating factor; BMI = body mass index.

Table II. Comparison of baseline data between two groups.

Group	n	Complete remission	Partial remission	Unrelieved	Total remission rate
Combined group	64	36 (56.25)	18 (28.13)	10 (15.63)	54 (84.38)
HAG group	61	22 (34.38)	20 (31.25)	19 (29.69)	42 (65.63)
χ^2					4.224
p					0.040

HAG = homoharringtonine + cytarabine + granulocyte colony-stimulating factor.

Table III. Comparison of immune function between two groups.

Time	Group	n	CD4⁺ (%)	CD8⁺ (%)	CD4⁺/CD8⁺
Before treatment	Combined group	64	32.80±5.11	32.06±4.99	1.01 (1.01-1.03)
	HAG group	61	31.36±5.82	30.44±6.45	1.01 (1.00-1.10)
	t/Z		1.472	1.557	-1.203
	p		0.143	0.122	0.229
After treatment	Combined group	64	41.63±5.61#	24.91±4.01#	1.70±0.26#
	HAG group	61	37.29±5.89#	26.85±6.37#	1.43±0.22#
	t		4.216	-2.027	6.185
	p		<0.001	0.045	<0.001

Compared with the same group before treatment, #p<0.05. HAG = homoharringtonine + cytarabine + granulocyte colony-stimulating factor.

the HAG group. There was no statistically significant difference in baseline data between the two groups of patients ($p > 0.05$) (Table I).

The total response rate of the combined group (84.38%) was higher than that of the HAG group (65.63%) ($p < 0.05$) (Table II).

Before the treatment, there was no significant difference between the two groups in the levels of CD4+, CD8+, and CD4+/CD8+ ($p > 0.05$). After the treatment, levels of CD4+ and CD4+/CD8+ in both groups increased compared to pre-treatment levels and were significantly higher in the combined group compared to the HAG group. Levels of CD8+ after the treatment decreased and were significantly lower in the combined group than in the HAG group ($p < 0.05$) (Table III).

Similarly, there was no significant difference in bFGF and VEGF levels between the two groups before the treatment ($p > 0.05$). After the treatment, the levels of bFGF and VEGF in both groups decreased and were markedly lower in the combined group compared to the HAG group ($p < 0.05$) (Table IV).

There was no significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$) (Table V).

Table IV. Comparison of bFGF and VEGF levels between two groups (pg/ml).

Time	Group	n	bFGF	VEGF
Before treatment	Combined group	64	133.14±17.78	132.42±13.87
	HAG group	61	131.13±17.15	130.03±17.48
	t/Z		0.642	0.849
	p		0.522	0.398
After treatment	Combined group	64	98.67±13.21#	95.28±11.58#
	HAG group	61	110.02±12.81#	109.20±13.54#
	t		-4.871	-6.185
	p		<0.001	<0.001

Compared with the same group before treatment, #p<0.05. HAG = homoharringtonine + cytarabine + granulocyte colony-stimulating factor; bFGF = basic fibroblast growth factor; VEGF = vascular endothelial growth factor

Discussion

Our results show that the combined decitabine/HAG regimen can significantly improve the effectiveness of AML treatment, better regulate the immune function of AML patients, and improve the overall intervention effect of the treatment, without increasing the risk of adverse reactions. HAG regimen is a commonly used chemotherapy regimen for the treatment of AML in clinical practice. Granulocyte colony-stimulating factor can promote tumor cells to enter the proliferation cycle and significantly enhance the sensitivity of leukemia cells to chemotherapy drugs[6-11]. Mi et al[12] showed in a review of that homoharringtonine is a reliable choice for treating AML patients under the age of 60, with a low recurrence rate. Xie et al[8] found in a meta-analysis of 2314 AML patients that the HAG regimen is an effective and safe treatment for AML, more effective and tolerable than chemotherapy. Our results are consistent with previous studies stating that dicitabine is currently the most potent specific DNA methyltransferase inhibitor known[9,10]. Huang et al[13] showed that the comprehensive treatment of elderly AML patients with decitabine combined with HAG can effectively improve the overall effective rate and remission rate of disease treatment, without increasing the risk of toxic side effects. DiNardo et al[14] also showed that using decitabine on the basis of conventional regimens for the treatment of acute myeloid leukemia improved the overall treatment effect. Chen et al[15] confirmed that decitabine can upregulate SH3 domain-binding glutamic acid-rich-like protein, thereby promoting apoptosis of leukemia cells and improving disease treatment efficacy. Pollyea et al[16] pointed out that the pathogenesis of leukemia is related to gene mutations, chromosomal abnormalities, and epigenetic changes (including chromatin remodeling, DNA methylation, etc.). DNA methylation is a research focus, and it is clinically believed to be a dynamic and reversible process[16,17]. Decitabine is an adenosine analog which can replace cytosine in tumors at low concentrations and covalently bind to DNA methyltransferase. This interaction causes the enzyme to lose its activity and restores normal cell function, including terminal differentiation, aging and apoptosis, thus enhancing the self-renewal ability of hematopoietic stem cells[11,16-18].

Numerous studies[19-21] showed that VEGF has a mitogenic effect on vascular endothelial cells, and can regulate angiogenesis, accelerate the growth and proliferation of tumor cells, enhance vascu-

Table V. Comparison of bFGF and VEGF levels between two groups (pg/ml).

Group	n	Heating	Infect	Abnormal liver function	Gastrointestinal reactions
Combined group	64	19 (29.69)	17 (26.56)	16 (25.00)	26 (40.63)
HAG group	61	20 (31.25)	15 (23.44)	17 (26.56)	24 (37.50)
χ^2		0.140	0.064	0.132	0.021
p		0.709	0.801	0.716	0.884

HAG = homoharringtonine + cytarabine + granulocyte colony-stimulating factor.

lar permeability, and stimulate the division of vascular endothelial cells. Studies[19,20] show that increased VEGF levels in leukemia patients are mainly due to excessive proliferation of leukemia cells in bone marrow, and subsequent increase in the tumor load. This leads to increased secretion of hypoxia-inducible factors, further increasing VEGF expression, accelerating angiogenesis, and promoting leukemia progression[20]. BFGF has the function of promoting angiogenesis and can play a synergistic role with VEGF[20,21]. The results of our study showed that the levels of bFGF and VEGF in patients who received the combined treatment were lower than in patients who were treated by HAG alone, further confirming the high application value of decitabine and HAG in the treatment of AML. We may speculate that the combination therapy allows to effectively maintain a high methylation state of DNA replication, thus inhibiting the proliferation of white blood cells and downregulating the expression of bFGF and VEGF[22,23].

Limitations

This is a single-center retrospective analysis with a small sample size. Only patients with complete clinical data were included, resulting in selection bias. Additionally, there was no long-term follow-up to assess the survival rate. Future prospective studies with large sample sizes and long-term follow-up are needed to confirm the conclusions of this study.

Conclusions

Compared to the HAG regimen alone, the combination of decitabine and HAG is safe and is associated with higher treatment efficiency. It can significantly improve the immune function of AML patients and regulate bFGF and VEGF levels without increasing the risk of adverse effects.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

KY conceived and designed the study. SX, HC, SC, and TJ collected the data and performed the analysis. KY was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval

The ethics committee of our hospital approved this study on May 23rd, 2023, No. NYL2022106.

Informed Consent

Patient informed consent was obtained.

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