

# Analysis of efficacy, safety and prognostic factors of DAC-HAA treatment in Chinese pediatric patients with refractory or relapsed acute myeloid leukemia

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**Abstract.** Hematopoietic stem cell transplantation (HSCT) is generally considered as the only effective treatment for children with relapsed/refractory (R/R) acute myeloid leukemia (AML). Achieving remission prior to HSCT affects the efficacy of the procedure and patient survival; therefore, induction therapy in children with R/R AML prior to HSCT is very important. The aim of the present study was to evaluate the clinical efficacy, prognosis and safety of 5-aza-2-deoxycytidine (DAC) combined with homoharringtonine + cytarabine + aclarubicin (HAA regimen) in the treatment of pediatric R/R AML. A total of 53 pediatric patients with R/R AML, aged 1-14 years, were treated with DAC-HAA. The overall response rate was 83.1%, with a complete remission rate of 77.4% and a partial remission rate of 5.7%. In conclusion, DAC-HAA therapy for children with R/R AML was found to be associated with a high remission rate, a short period of bone marrow suppression and a good safety profile. Therefore, DAC-HAA may be of value as a transitional regimen prior to HSCT and is worthy of clinical consideration.

## Introduction

Although significant advances in chemotherapy for childhood acute myeloid leukemia (AML) have been made in recent years, 50-70% of all pediatric patients relapse after achieving the first complete remission (CR) (1-4). In addition, the long-term disease-free survival rate is only ~40% (5). It is generally

believed that hematopoietic stem cell transplantation (HSCT) is currently the only effective treatment for pediatric relapsed/refractory (R/R) AML (6). However, whether the patient has achieved remission prior to the transplantation procedure markedly affects the efficacy of the treatment and patient survival after transplantation; therefore, induction therapy prior to HSCT is very important for pediatric patients with R/R AML.

The clinical CR rate of treatment with homoharringtonine (HHT) + cytarabine (Ara-C) + aclarubicin (Acla) (HAA regimen) in adults with R/R AML has been previously reported to be as high as 80% (7). Therefore, the present retrospective study was conducted to investigate whether treatment with HAA combined with 5-aza-2-deoxycytidine (DAC) can improve the clinical remission rate in pediatric patients with R/R AML.

## Patients and methods

**Patients.** To retrospectively evaluate the clinical efficacy, prognosis and safety of DAC combined with HAA in the treatment of R/R AML in pediatric patients, a total of 53 children with R/R AML (except M3 type) admitted to the Department of Hematology of Anhui Provincial Cancer Hospital (Hefei, China) between May 2010 and May 2020 were included in the present study. All patients were diagnosed based on the morphology, immunophenotype, cytogenetics and molecular biology classification criteria (8). All parents/legal guardians of the patients provided written informed consent forms, and the study was approved by the Ethics Committee of the Anhui Provincial Cancer Hospital (no. 2021-EXK-02) and complied with the ethical guidelines outlined in the 1975 Helsinki Declaration. The standard of relapse was defined as follows: After CR, leukemic cells reappearing in the peripheral blood, or >5.0% blast cells in the bone marrow (after excluding other reasons, such as bone marrow regeneration after consolidation chemotherapy), or extramedullary leukemic cell infiltration.

**Treatment.** All patients were treated with DAC-HAA according to disease conditions and the patients' compliance. The detailed DAC-HAA regimen was as follows: DAC (20 mg/m<sup>2</sup>, qd,

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days 1-3), HHT (2 mg/m<sup>2</sup>, qd, days 4-10), Ara-C (100 mg/m<sup>2</sup>, q12h, days 4-10) and Acla (12 mg/m<sup>2</sup>, qd, days 4-10).

**Statistical analysis.** Fisher's exact test was used to detect the factors that influenced the CR rate. Kaplan Meier curve analysis was used to detect the factors that influenced the overall survival rate. The statistical analysis was performed using SPSS software, version 19 (SPSS, Inc.). P<0.05 was considered to indicate a statistically significant difference.

## Results

**Patient characteristics.** The characteristics of the patients are summarized in Table I. A total of 53 patients were enrolled in the present study, including 23 female and 30 male patients. The median age of the patients was 7 years (range, 1-14 years). A total of 15 patients were diagnosed with relapsed AML, and 38 patients were diagnosed with refractory AML. According to the WHO classification (8), 6 patients had a diagnosis of M1, 23 patients had a diagnosis of M2, 4 patients had a diagnosis of M4, 13 patients had a diagnosis of M5, 2 patients had a diagnosis of M6, and 5 patients had a diagnosis of M7. A total of 2 patients had FMS-like tyrosine kinase 3-internal tandem duplication mutations, 16 patients had t(8:21) mutations, 16 patients had AML1-ETO mutations, and 2 patients had mixed lineage leukemia-AF9 mutations. Furthermore, 42 of these patients had undergone HSCT.

**Response and treatment outcome.** A total of 41/53 patients (77.4%) achieved CR after the first course of induction treatment, and PR was observed in 3 patients (5.7%), with an overall response rate of 83.1%. Patients were divided into different subgroups to analyze the association of CR with various factors. As shown in Table II, t(8:21) had a slight favorable effect on CR rate, as patients with t(8:21) had a CR rate of 88 vs. 73% in patients without this mutation. The analysis demonstrated that age, sex, white blood cell count, platelet count, hemoglobin concentration and disease status exerted no significant effect on CR rate. Clinically, the prognosis of patients with refractory AML is often worse compared with that of patients with recurrent AML (9). The present study demonstrated that the CR rate of refractory patients is similar to that of recurrent patients, indicating that DAC-HAA also has an excellent therapeutic effect in patients with refractory disease. Kaplan-Meier curve analysis of the factors that influenced overall survival indicated that t(8:21) and HSCT had a positive impact on survival. On the other hand, sex, age, and disease status did not significantly affect survival (Fig. 1).

**Toxicity.** Bone marrow suppression was evident in all children after chemotherapy. The mean time between the end of chemotherapy and the beginning of bone marrow hematopoiesis (neutrophil count  $\geq 0.5 \times 10^9/l$ ) was  $18.8 \pm 4.32$  days; during the period from the end of chemotherapy until the neutrophil count reached  $\geq 0.5 \times 10^9/l$ , the patients received red blood cell and platelet transfusions. The ratio of red blood cell and platelet volume to body weight was  $19.02 \pm 5.81$  ml/kg and  $0.156 \pm 0.065$  U/kg, respectively.

A total of 11 patients in this study developed grade 4 bone marrow suppression after treatment. The median time for

Table I. Patient characteristics (n=53).

Characteristics	No.
Sex (male/female)	30/23
Median age, years (range)	7 (1-14)
WHO classification subtype	
M1	6
M2	23
M3	0
M4	4
M5	13
M6	2
M7	5
Genetic anomaly at initial diagnosis	
Normal karyotype without any molecular abnormality	10
FMS-like tyrosine kinase 3-internal tandem duplication	2
t(8:21)	16
AML1-ETO	16
Mixed lineage leukemia-AF9	2
Disease status	
Relapsed	15
Refractory	38
White blood cell count, $\times 10^9/l$	
<10	13
$\geq 10$	40
Platelet count, $\times 10^9/l$	
$\leq 50$	31
>50	22
Hemoglobin concentration, g/l	
$\leq 100$	33
>100	20
Hematopoietic stem cell transplantation	
Yes	42
No	11

granulocyte recovery (neutrophil count  $0.5 \times 10^9/l$ ) in 4 patients with CR was 14 days (range, 7-25 days), and the median time for platelet recovery (platelet count  $20 \times 10^9/l$ ) was 23 days (range, 7-37 days). Fever occurred in 11 patients during granulocytopenia, including pulmonary infection in 5 patients, septicemia in 4 patients, skin and soft tissue infection in 1 patient, herpes zoster infection in 1 patient and acute otitis media in 1 patient. In 1 patient, pulmonary infection combined with alveolar hemorrhage resulted in a fatal outcome following failure of anti-infection treatment, while the symptoms in the remaining patients disappeared after successful anti-infection treatment.

Idarubicin (IDA) combined with high-dose Ara-C (IA) and HHT are known to be associated with cardiotoxicity (10). Therefore, all patients in the present study also received cardioprotective treatment with vitamin C and coenzyme Q10 at the same time as chemotherapy. No obvious cardiotoxicity was found during or after chemotherapy, and no obvious

Table II. CR analysis.

Characteristics	CR/total, n	CR rate (%)	P-value
Sex			0.323
Male	22/30	73	
Female	19/23	83	
Age, years			0.542
<5	12/15	80	
≥5	29/38	76	
WHO classification subtype			0.253
M1-M4	27/33	82	
M5-M7	14/20	70	
Genetic anomaly at initial diagnosis			0.215
t(8:21)	14/16	88	
Normal	27/37	73	
White blood cell count, $\times 10^9/l$			0.619
<10	10/13	77	
≥10	31/40	78	
Platelet count, $\times 10^9/l$			0.362
≤50	25/31	81	
>50	16/22	73	
Hemoglobin concentration, g/l			0.499
≤100	25/33	76	
>100	16/20	80	
Disease status			0.542
Relapsed	12/15	80	
Refractory	29/38	76	

CR, complete remission.

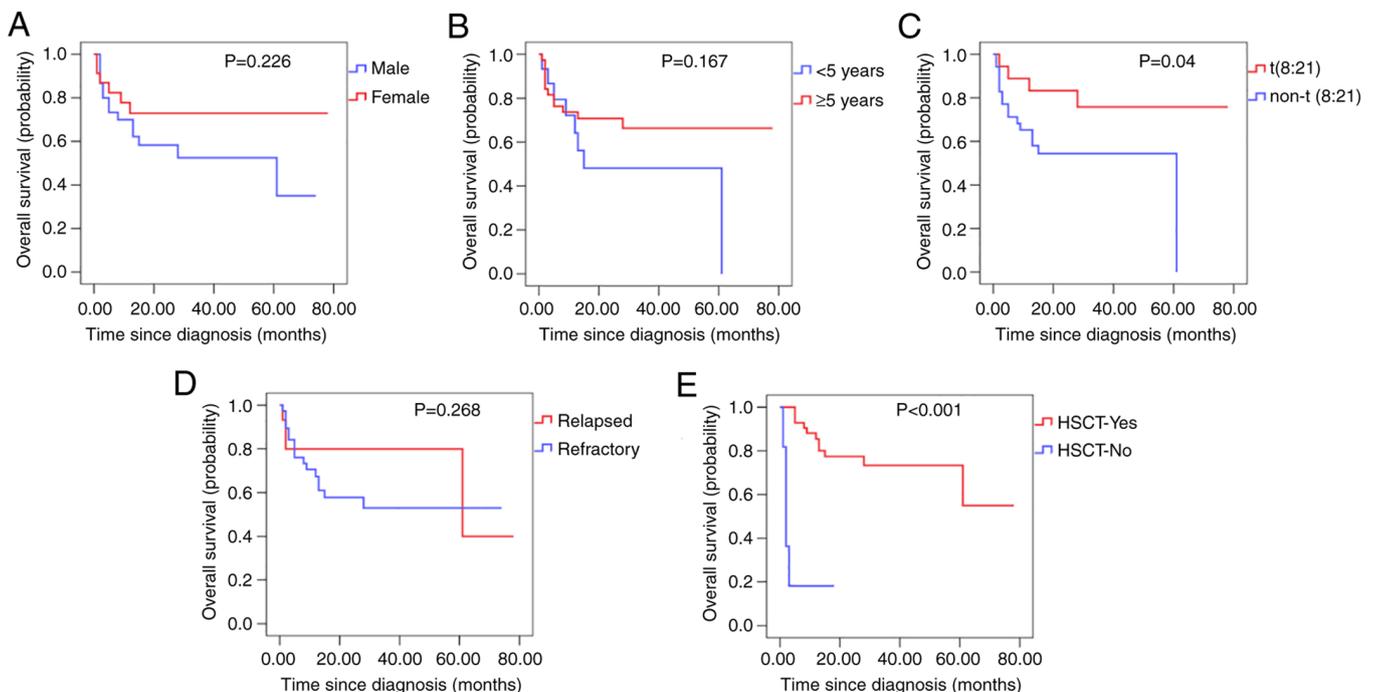


Figure 1. Kaplan-Meier curve analysis of patient overall survival by different clinicopathological characteristics. (A) Sex (male vs. female). (B) Age (&lt;5 vs. ≥5 years). (C) t(8:21) mutation status. (D) Relapsed vs. refractory disease. (E) HSCT (yes vs. no). HSCT, hematopoietic stem cell transplantation.

abnormalities were observed in the electrocardiogram. A total of 66.0% of the patients developed infections of different severity, mainly manifesting as pneumonia (80%), of which 67.9% of the cases were caused by bacteria, 17.8% were caused by fungi and 14.3% had a mixed etiology.

Other non-hematological adverse reactions included nausea (n=10; 19%), vomiting (n=14; 26%), diarrhea (n=7; 13%), mucositis (n=4; 7%) and constipation (n=14; 26%), which improved with symptomatic treatment. A total of 4 patients developed reversible liver function abnormalities during chemotherapy, and no patient developed kidney damage.

## Discussion

Children with R/R AML have poor outcome and unfavorable response to chemotherapy, whereas the currently accepted radical therapy is HSCT (11). Whether the proportion of blasts in the bone marrow of the patient is <5% prior to transplantation plays a key role in the efficacy of transplantation and long-term survival; however, most conventional chemotherapy regimens cannot achieve bone marrow remission in children with R/R AML. Effective chemotherapy regimens mainly include the following: High-dose Ara-C, mitoxantrone + etoposide + Ara-C (MEC), fludarabine + Ara-C + granulocyte colony-stimulating factor (G-CSF) + IDA (FLAG-IDA) and Ara-C + aclarubicin + G-CSF (CAG), among others (12-14). The response rate with high-dose Ara-C chemotherapy is ~20% in R/R AML (15). The CR rate with FLAG-IDA is 52.1% (16). MEC is also occasionally used as the primary regimen in patients with R/R-AML, with CR rates of 18-66% (17).

In China, the treatment of children with R/R AML mostly includes IA, CAG or FLAG. Daunorubicin is an antitumor drug, which can inhibit the synthesis of RNA and DNA, has a wide antitumor spectrum and is mainly suitable for AML (18). The methoxy group is removed from the C4 position of the daunorubicin glycosidic group to form IDA. The structural change increases the lipophilicity of IDA, making it easier for the drug to penetrate cell membranes. In cells, IDA is metabolized to alcohol 4-demethoxydaunorubicin (IDAol). Compared with IDA, IDAol has the same antitumor activity with a markedly longer clearance time from the body, and it can penetrate through the blood-brain barrier and placenta. Compared to other anthracycline drugs, IDA has higher antitumor activity and can effectively reduce tumor recurrence rates (19-21). The application of IA chemotherapy in children with R/R AML is associated with a higher rate of bone marrow remission (22). However, when our team applied the IA regimen in the clinical setting, the total remission rate was found to be suboptimal, with a long bone marrow suppression period, high infection rate (100%) and high infection-related mortality rate.

In recent years, it has been found that abnormal DNA methylation plays an important role in the occurrence and development of AML. Demethylating agents, such as DAC and azacitidine, have been used in the treatment of adult R/R AML with good clinical efficacy (23-26). DAC is a highly effective inhibitor of DNA methyltransferase interfering with DNA methylation, which can reverse the DNA methylation process and activate silent tumor suppressor genes to inhibit the proliferation of tumor cells (27). Qin *et al* (28) found that, when combined with Ara-C, DAC can enhance its cytotoxicity.

HHT is an alkaloid antitumor drug extracted from the *Cephalotaxus* plant (29), and is able to inhibit the synthesis of DNA and protein in tumor cells with no cross-resistance with Ara-C. In addition, Zhou *et al* (30) reported that HHT and Ara-C also exert a synergistic effect; in particular, HHT combined with Acla and Ara-C (DAC-HAA) was able to achieve a high remission rate in adult R/R AML in previous reports (31,32).

To the best of our knowledge, there are yet no reports of this method applied as clinical treatment of children with R/R AML. The present study was undertaken to explore the efficacy, safety and prognostic factors of DAC-HAA treatment in Chinese pediatric patients with R/R AML. The results demonstrated that DAC-HAA achieved higher bone marrow remission rate, shorter bone marrow suppression period and higher disease-free survival rate, compared with DAC or HAA alone.

However, due to the small number of patients in the present study, and due to the fact that there were only 3 cases of patients with partial remission, it is impossible to systematically analyze the factors that may affect partial remission, which is a limitation of the present study. We hope that there will be a larger sample of clinical studies in the future, which enable the evaluation of the clinical efficacy of DAC-HAA in a more systematic and comprehensive manner.

In summary, the present results suggest that the DAC-HAA chemotherapy regimen is associated with a high bone marrow remission rate and a good safety profile in the treatment of pediatric patients with R/R AML, it may represent a good bridging treatment for HSCT, and is worthy of clinical consideration.

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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

Funding acquisition: LW; investigation: LW; resources: LW, BZ, CLiao; data curation: LW, FX, FC, SW, LC, NL; formal analysis: CLi; methodology: HL, CLi; project administration: HL, CLi; writing-review and editing: JW; supervision: HL. HL and CLi confirm the authenticity of the raw data. All the authors have read and approved the final manuscript.

## Ethics approval and consent to participate

All parents/legal guardians of the patients provided written informed consent forms, and the study was approved by the Ethics Committee of the Anhui Provincial Cancer Hospital

(no. 2021-EXK-02) and complied with the ethical guidelines of the 1975 Helsinki Declaration.

### Patient consent for publication

Not applicable.

### Competing interests

The authors that they have no competing interests.

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