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Original Article

DNMT3A R882 mutation in children with acute myeloid leukemia and its role in prognosis

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Abstract: Objective: To investigate the DNMT3A R882 mutation in children with acute myeloid leukemia (AML) and its effect on prognosis. Methods: A total of 148 children with AML treated in our hospital (March 2017 and March 2020) were selected for this study. According to the detection results of DNMT3A R882 mutations, the children were assigned into the mutation group (n = 20) and the non-mutation group (n = 128). The correlation of DNMT3A R882 mutation and non-mutation with other gene mutations in the children was observed; the clinical characteristics and cellular immune phenotype, as well as clinical remission rate, recurrence rate (RR) and overall survival (OS) after treatment were compared. Results: By genetic mutation detection, there were 20 cases (13.51%) with DNMT3A R882 mutation and 128 cases (86.49%) without DNMT3A R882 mutation among the children with 148 AML; the DNMT3A and NPM1 mutations were similar in the two groups (P > 0.05). The difference in the CEBPA mutation, FLT3-ITD mutation, and double mutation of FLT3-ITD and CEBPA was statistically significant between the two groups (P < 0.05). The white blood cell count, hemoglobin, and platelet levels in the DNMT3A R882 mutant group were higher than those in the non-mutation group (P < 0.05). The positive detection rates of CD15 (80.00%) and CD33 (75.00%) were increased in the DNMT3A R882 mutation group compared with the non-mutation group (35.16% vs 36.72%), whereas the detection rate of CD34 (7.50%) was reduced (P < 0.05). After treatment, the RR (90%) was significantly higher in the DNMT3A R882 mutation group than in the non-mutation group (13.28%), but the OS and disease-free survival (DFS) in the DNMT3A R882 mutation group were shorter than those in the non-mutation group (P < 0.05). The survival time in the DNMT3A R882 mutation group was shorter than that in the non-mutation group (χ^2 = 2.720, *P* = 0.032). WBC, PLT, HIB, CD15, CD34, and CD33 were independent risk factors for AML in the mutation group. Conclusion: DNMT3A R882 mutation is a common expression method of DNMT3A in AML. Children with DNMT3A R882 mutations have a higher white blood cell count, hemoglobin, and platelet levels. The cellular immune phenotypes CD15, CD33 are highly expressed, CD34 is lowly expressed, and DNMT3A R882 mutation may be associated with a poor prognosis in AML patients.

Keywords: Acute myeloid leukemia, DNMT3A R882 mutation, prognosis

Introduction

Acute myeloid leukemia (AML) is a malignant clonal hematologic disease derived from blood stem cells. It is more common in children, contributing to approximately 20% of childhood leukemia, and it greatly threatens the quality of life and health of children [1]. With the development of genetic understanding and the improvement of various technologies such as gene sequencing and PCR, great progress has been made in the treatment of children with AML in clinical practice, and the three-year overall survival (OS) rate is as high as 60%-75%. However, since the initial treatment is not yet effective in some children, the recurrence rate (RR) is higher in children with initial remission [2]. Therefore, the search for effective and novel diagnostic criteria and prognostic markers plays an essential role in the early selection of more effective regimens for children with AML. It has been found [3, 4] that DNA methyltransferase 3A (DNMT3A) gene mutations, a group of genes encoding the protein DNMT3A, are strongly associated with AML prognosis in patients with AML, and they function in the growth and development of the organism, maintaining the length of telomere, regulating genet-

ic expression levels and sustaining the stable length of the chromosome itself. Abnormal methylation has the potential to affect DNA replication, recombination, and repair, which affects the development of embryonic stem cell and leads to tumorigenesis [5]. Studies have shown [6] that abnormal expression of CD antigen in stem cells of AML patients also affects the prognosis. Most of the clinical studies on AML gene mutations have focused on adults, and less investigation has been conducted on the characteristics of gene mutations in children with AML. As a consequence, the present study was conducted on 148 children with AML who were admitted to our hospital (March 2017 to March 2020) so as to investigate the clinicopathological features and prognosis of survival in children with DNMT3A R882 mutations.

Materials and methods

General data

A total of 148 children with treatment-naive AML who underwent DNMT3A R882 mutation monitoring in our hospital between March 2017 and March 2020 were selected. Inclusion criteria: (1) children who were diagnosed with AML by immunology, bone marrow morphology, cytomorphology and DNA genes; (2) the diagnosis referred to the "Diagnostic and Therapeutic Criteria of Hematologic Diseases" edited by Zhang Zhinan [7]; (3) all children were initially diagnosed with AML; (4) children were aged ≤ 14 years old; (5) children or parents signed the informed consent form. Exclusion criteria: (1) the presence of severe heart, kidney, liver and other organ dysfunction; (2) acute mixed lineage leukemia. This study obtained the approval from the Ethics Committee of our hospital.

Methods

Gene mutation detection: Three ml of peripheral blood was collected from all children in a fasting state in the morning, centrifuged and cryopreserved (-80°C). Afterwards, the amplified products were subjected to gene sequencing using a gradient polymerase chain reaction (PCR) (Dongsheng International Trading Co., Ltd.) amplification instrument. The detected genes included CEBPA, DNMT3A, FLT3-ITD, NPM1 and FLT3-ITD. ABI 3130 automated genetic analyzer from Applied Biosystems (USA) was used for leukemia prognosis gene detection by gene sequencing. The reagents were supplied by Shanghai Yuanqi Bio-Pharmaceutical Co., Ltd. They were assigned into the mutation group (n = 20) and non-mutation group (n = 128) based on the detection results of the DNMT3A R882 mutation.

Cellular immunophenotype: The children's serum was used to detect, by FC50 flow cytometry, CD14, CD15, CD33, CD64, CD38, CD58, CD11b, CD117, CD56, CD34, HLA-DR, and MPO antigens. The immune phenotype of leukemia cells was analyzed by CD45/SSC gate. The proportion of children with antigen-positive expression was calculated based on the WHO definition of antigen expression of ≥ 20% as positive expression.

Treatment and follow-up: All children were administered MA/DA/IA or high-dose (q12 h, 1-3 g/m^2) arabinoside as monotherapy for induction and chemotherapy according to the induction remission regimen in adults. After remission induction, intensive treatment with HD-Ara-C for 5 cycles was administered for consolidation therapy, followed by maintenance therapy. All children were followed up until March 2020 to observe recurrence, disease progression, change of treatment regimen and death.

Observation indicators

(1) The correlation of DNMT3A R882 mutation or non-mutation with other gene mutations in children was observed; (2) The comparison of clinical characteristics of children was conducted in the DNMT3A R882 mutation group and non-mutation group; (3) The comparison of cellular immune phenotypes in children was performed in the DNMT3A R882 mutation group and non-mutation group; (4) The comparison of clinical remission rate after treatment in children was carried out in the DNMT3A R882 mutation group and non-mutation group. Disease classification was defined by the Diagnostic and Therapeutic Criteria of Hematologic Diseases [7] as follows: ① complete remission (CR): children had no clinical symptoms caused by leukemia cell invasion, with their bone marrow blasts were ≤ 5%, and platelet count was ≥ 100 × 10^9/L; ② partial remission (PR): children still had clinical symptoms caused by leukocyte invasion; ③ no remission: clinical symptoms of children did not change significantly, or even

Table 1. Correlation of DNMT3A R882 mutation and non-mutation with other gene mutations

Group	CEBPA mutation	FLT3-ITD mutation	NPM1 mutation	FLT3-ITD
Mutation group (n = 20)	7 (35.00)	10 (50.00)	2 (1.00)	5 (25.00)
Non-mutation group (n = 128)	18 (14.06)	22 (17.19)	15 (11.72)	7 (5.49)
χ^2	5.401	10.989	0.505	8.856
P	0.020	0.001	0.823	0.003

Table 2. Comparison of the clinical characteristics between the two groups

Clinical characteristics	Mutation group (n = 20)	Non-mutation group (n = 128)	t/χ^2	*P*
Gender			0.082	0.775
Male	11 (14.29)	66 (85.71)		
Female	9 (12.68)	62 (87.32)		
Age (year)			0.014	0.905
< 6	8 (13.11)	53 (86.89)		
6-14	12 (13.79)	75 (86.21)		
White blood cell count ($\times 10^9$/L)	45.70±14.02	25.84±10.05	7.755	< 0.001
Number of bone marrow blasts	52.64±12.55	52.55±12.80	0.029	0.977
Hemoglobin (g/L)	78.80±25.22	65.43±20.37	2.642	0.009
Platelet ($\times 10^9$/L)	70.96±25.46	39.58±19.24	10.670	< 0.001
FAB classification			0.088	0.644
Low-risk	6 (12.77)	41 (53.24)		
Medium-risk	9 (16.67)	45 (83.33)		
High-risk	5 (10.34)	42 (89.37)		

aggravated, with their bone marrow blasts ≥ 20%. Remission rate = (CR+PR)/total cases × 100%. (5) The RR, OS and disease-free survival (DFS) after treatment in children were compared.

Statistical analysis

SPSS 19.0 software was used to process the study data. The quantitative data were presented as ($\bar{x} \pm s$), and the standalone sample t-test was used. The qualitative data were presented as n (%), and the χ^2 test was used. The survival curves were plotted by the Kaplan-Meier method in the two groups, and the log-rank test was performed at a significant level of $\alpha = 0.05$. Logistic multivariate regression analysis for AML in the mutation group was performed. $P < 0.05$ suggested a statistically significant difference.

Results

Correlation of DNMT3A R882 mutation and non-mutation with other gene mutations

By genetic mutation detection, there were 20 cases (13.51%) with DNMT3A R882 mutation and 128 cases (86.49%) without DNMT3A R882 mutation among the 148 AML children. There were no statistically significant differences in DNMT3A and NPM1 mutations between the DNMT3A R882 mutation group and non-mutation group ($P > 0.05$). The CEBPA mutation, FLT3-ITD mutation, and double mutation of FLT3-ITD and CEBPA were statistically different in the two groups ($P < 0.05$) (**Table 1**).

Comparison of clinical characteristics

No statistically significant differences in gender, age, number of bone marrow blasts, and FAB classification of acute leukemia were observed between the DNMT3A R882 mutation group and non-mutation group ($P > 0.05$). The levels of white blood cell count, hemoglobin, and platelets were increased in the DNMT3A R882 mutation group in relation to the non-mutation group ($P < 0.05$) (**Table 2**).

Comparison of cellular immunophenotype

The positive detection rates of CD15 and CD33 (80.00% and 75.00%) were increased in the DNMT3A R882 mutation group compared with the non-mutation group (35.16% and 36.72%),

Table 3. Comparison of cellular immunophenotype of children between the DNMT3A R882 mutation group and non-mutation group

CD antigen	Mutation group (n = 20)	Non-mutation group (n = 128)	χ^2	*P*
CD14	9 (45.00)	82 (64.06)	2.654	0.103
CD15	16 (80.00)	45 (35.16)	14.357	< 0.001
CD33	15 (75.00)	47 (36.72)	6.465	0.001
CD64	12 (60.00)	88 (68.75)	0.604	0.437
CD38	15 (75.00)	90 (70.31)	0.184	0.668
CD58	6 (30.00)	56 (43.75)	1.343	0.246
CD11b	6 (30.00)	50 (39.06)	0.604	0.437
CD117	17 (85.00)	92 (71.88)	1.535	0.215
CD56	8 (40.00)	49 (38.28)	0.022	0.883
CD34	6 (7.50)	74 (92.50)	5.387	0.020
HLA-DR	16 (80.00)	87 (67.97)	1.183	0.277
MPO	13 (65.00)	87 (67.97)	0.070	0.792

but the detection rate of CD34 (7.50%) was decreased in relation to the non-mutation group (92.50%) ($P < 0.05$). No statistically significant difference was found in other detection antigens of children with positive DNMT3A R882 mutation between the two groups ($P > 0.05$). See **Table 3**.

Comparison of clinical remission rate

No statistically significant difference was observed in clinical remission rate of children between the NMT3A R882 mutation group and non-mutation group ($P > 0.05$, **Table 4**).

Comparison of the RR and OS after treatment in children

After treatment, the RR (90%) was remarkably higher in the DNMT3A R882 mutation group than in the non-mutation group (13.28%), whereas the OS and DFS were shorter in the DNMT3A R882 mutation group than in the non-mutation group ($P < 0.05$) (**Table 5**). The results of survival analysis by the Kaplan-Meier revealed that the survival time in the DNMT3A R882 mutation group was shorter than that in the non-mutation group ($\chi^2 = 2.720$, $P = 0.032$). The factors with statistical difference were assigned as an independent variable, and the logistics multivariate regression analysis was performed. The results showed that WBC, PLT, HIB, CD15, CD34, and CD33 were independent risk factors for AML in the mutation group. (**Figure 1** and **Table 6**).

Discussion

AML is the most common childhood leukemia, which often leads to increased white blood cell count, thrombocytopenia and decreased hemoglobin. Due to uncontrolled differentiation and proliferation of red blood cells in the bone marrow of patients, the blood cells with normal function are reduced, and leukemia cells continue to proliferate, resulting in clinical symptoms such as anemia, bleeding, infection and extramedullary tissue and organ infiltration in patients [8, 9]. The disease has a high degree of deterioration, rapid development, low survival rate, and dangerous prognosis, which gravely threatens the life and health of these children [10]. At present, the influencing factors and pathogenesis of AML have not been fully clarified in clinical practice, and some scholars believe that the occurrence of the disease is related to the presence of immune dysfunction, viral infection and even ionizing radiation in children [11, 12]. Relevant studies [13] have shown that the prognosis of children with AML is strongly linked to their white blood cell count and molecular biological parameters. Therefore, exploring the pathogenesis of children with AML is of great significance to clinical medication and early selection of treatment regimens.

With intensive research into the molecular biology and genetics of leukemia along with the improvement of gene sequencing and PCR, more attention has been paid to gene mutations and epigenetic alterations in children with AML. In recent studies [14], DNMT3A was found to be a high-frequency mutation in AML patients, including V897D, R478W, R882, and G543C, of which 60% were R882 site mutations. The DNMT3A R882 mutation disrupts the dimer interface within DNMT3A, but the resulting DNMT3A tetrameric complex still has certain activity. Nonetheless, the disruption of the dimer interface enables DNMT3A to separate from DNA, and causes reduced DNA methylation, which are associated with the decreases in catalytic activity of DNMT3A enzymes, the down-regulation of the expression of tumor suppressor genes such as p21 and p53, and up-regulation of the expression of oncogenes, leading to leukemia [15, 16]. Two-site mutations in CEBPA are more common in adult AML,

Table 4. Comparison of clinical remission rate of children between the two groups

Group	CR	PR	No remission	Remission rate
Mutation group (n = 20)	1 (5.00)	3 (15.00)	16 (80.00)	4 (20.00)
Non-mutation group (n = 128)	9 (7.03)	22 (17.19)	97 (75.78)	31 (24.22)
χ^2				0.170
P				0.680

Table 5. Comparison of the RR and OS after treatment in children between DNMT3A R882 mutation group and non-mutation group

Group	RR	OS (month)
Mutation group (n = 20)	18 (90.00)	12.42±2.24
Non-mutation group (n = 128)	17 (13.28)	22.43±4.02
t/χ^2	51.624	10.850
P	< 0.001	< 0.001

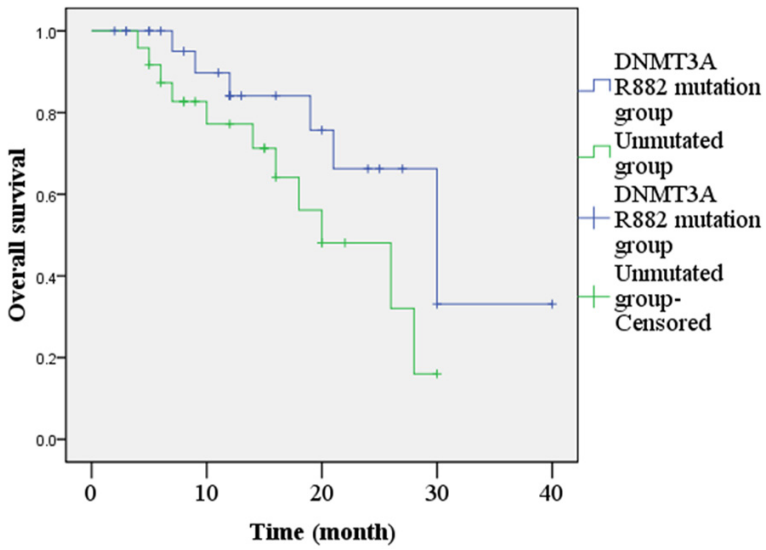

Figure 1. K-M survival curve of children in DNMT3A R882 mutation group and non-mutation group after treatment.

with a mutation rate ranging from 9.3% to 19.7%, while DNMT3A mutation is less common in AML children [17]. Furthermore, there are few reports studying AML in children. The mutation rate of DNMT3A R882 is 13.51% in light of the analytical results of 148 children in this study, indicating a low mutation rate of DNMT3A in AML children. Thol [18] et al. reported that by detecting mutations in the 23rd exon of DNMT3A in 195 children with AML, only two children were considered to have mutations in this gene and FLT3-ITD mutations. This has been found in adult myeloproliferative neoplasms, myelofibrosis, and myelodysplastic syndromes. The results of this study showed that 20 children (13.51%) with AML had DNMT3A R882 mutations detected by gene mutation, and the white blood cell count, hemoglobin and platelet levels in these children were higher than those in the non-mutation group, which was partially consistent with HOU et al. [19]. The number of bone marrow blasts was increased in the DNMT3A group. Although the number of bone marrow blasts was increased in the DNMT3A R882 mutation group in this study, it was not statistically significant compared with the non-mutation group. This may be due to the fact that the DNMT3A R882 mutation remains unclear due to the low prevalence of the disease in the children [20]; and there are diverse differences in methodology and the number of cases collected, and errors among experimental studies. The expression of cellular immune phenotypes can be used clinically to determine the extent and source of bone marrow cell development. In the present study, the positive detection rates of CD15 and CD33 in the DNMT3A R882 mutation group were higher than those in the non-mutation group, but the detection rate of CD34 was lower than that in the non-mutation group, which may be related to the differentiation or maturation of CD molecules on the cell surface. This study also indicated that there was no statistically significant difference in clinical remission rate of children between the DNMT3A R882 mutation group and non-mutation group, whereas the RR was higher in the mutation group (90%) than in the non-mutation group (13.28%), and the OS and

Table 6. Logistics multivariate regression analysis of independent risk factors for AML

Factors	β	SE	wald X^2	P	OR	95% CI
CEBPA mutation	-0.133	0.179	0.410	0.578	0.896	0.636~1.250
FLT3-ITD mutation	-0.006	0.004	2.485	0.133	0.844	0.613~1.001
FLT3-ITD	0.255	0.189	1.832	0.168	1.288	0.888~1.879
White blood cell count	0.633	0.261	4.774	0.02	1.896	1.171~3.114
Hemoglobin	1.104	0.239	17.256	0.001	2.655	1.734~4.451
Platelet	0.734	0.156	16.988	< 0.001	3.339	1.554~3.878
CD15	0.302	0.105	8.254	0.004	1.355	1.088~1.687
CD33	0.034	0.006	4.844	0.021	1.035	1.028~1.050
CD34	0.925	0.255	27.985	< 0.001	3.226	1.552~3.968

Note: Factor assignment: CEBPA mutation (Yes = 1, No = 0); FLT3-ITD mutation (Yes = 1, No = 0); FLT3-ITD (Yes = 1, No = 0); White blood cell count (Abnormal value = 1, normal value = 0); Hemoglobin (abnormal value = 1, normal value = 0); Platelet (abnormal value = 1, normal value = 0); CD15 (abnormal value = 1, normal value = 0); CD33 (abnormal value = 1, normal value = 0); CD34 (abnormal value = 1, normal value = 0).

DFS in the mutation group were shorter than those in the non-mutation group. It was suggested that DNMT3A R882 mutation may not affect the effectiveness of remission therapy by induction, but can cause children with AML to become resistant to chemotherapeutic agents, thereby leading to relapse and affecting the survival of the children. Therefore, this can serve as a prognostic factor in AML. The limitations of this research include the following: first, a relatively small sample size was used; second, the analysis was limited to patients in a hospital. Hence, caution should be taken in the interpretation of the results of the present study.

In summary, DNMT3A R882 mutation is a common expression of DNMT3A in AML. AML children with DNMT3A R882 mutation have high levels of white blood cells, hemoglobin and platelets, high expression of CD15 and CD33, and low expression of CD34 in cellular immunophenotypes. Moreover, DNMT3A R882 mutation is related to poor prognosis in AML patients.

Disclosure of conflict of interest

None.

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