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ORIGINAL ARTICLE

Risk factors and prognostic analysis of acute myeloid leukemia in children

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Summary

Purpose: *To explore the efficacy and related prognostic factors of acute myeloid leukemia (AML) in children except acute promyelocytic leukemia (APL).*

Methods: *The clinical data of 89 non-APL children with AML treated in our hospital were retrospectively analyzed. The remission status was analyzed after chemotherapy, the long-term survival was evaluated using the Kaplan-Meier method, and the influencing factors for the prognosis were detected using univariate and multivariate Cox regression analyses.*

Results: *Complete remission (CR) was realized in 71 cases (79.8%) after the first course of treatment, 13 cases (14.6%) after the second course of treatment, and 5 cases (5.6%) after the third course of treatment. The 5-year event-free survival (EFS) rate and overall survival (OS) rate were 53.9% and 66.3%, respectively. The children were divided into low-risk group (n=31), middle-risk group (n=36) and high-risk group (n=22). In the three groups, the 5-year OS rate was 74.2%, 72.2% and 45.5%, respectively, while the 5-year EFS rate was 67.7%, 55.6% and 31.8%, respectively. Extramedullary infiltration at the time of initial diagnosis [HR=3.313 (95% CI: 1.748-13.664)], $CD56^+$ [HR=1.592 (95% CI: 1.172-2.255)] and recurrence time <1 year [HR=3.040 (95% CI: 1.087-5.508)] were independent risk factors affecting the prognosis, and CR achieved after the first course [HR=0.786 (95% CI: 0.228-0.803)] was an independent factor improving the prognosis of patients.*

Conclusions: *The prognosis is poor in non-APL children with AML who have extramedullary infiltration at the time of initial diagnosis, $CD56^+$ and recurrence time <1 year, and CR achieved after the first course is an independent factor improving the prognosis of patients. The long-term EFS rate is significantly lower in high-risk group than that in low- and middle-risk groups. Intensive chemotherapy or early hematopoietic stem cell transplantation should be performed for high-risk patients.*

Key words: *acute myeloid leukemia, children, chemotherapy, efficacy, prognosis*

Introduction

Leukemia is the most common malignancy in childhood, dominated by acute lymphoblastic leukemia (ALL) (70%), followed by acute myeloid leukemia (AML) (20-30%) [1]. According to the morphological classification, AML is classified into 8 subtypes (M0-M7) by FAB Cooperation Group, in which M3 [acute promyelocytic leukemia (APL)] is a special type of AML. With the development of chemotherapy drugs, APL has become a curable hematological malignancy [2,3]. However, the long-term survival rate is about 40-60% in non-APL children with AML, lower than that of ALL in children (70-80%). More than one-third of non-APL children with AML have a poor prognosis, a high incidence rate of treatment-related complications and a high mortality [4-7].

In recent years, with the development of "high-intensity short-course" chemotherapy, the enhance-

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ment of supportive treatment and the application of hematopoietic stem cell transplantation (HSCT), the therapeutic effect on AML in children has been improved [8,9]. Understanding the related characteristics of disease and the influencing factors for prognosis is helpful for further improving the long-term efficacy. In this paper, non-APL children with AML treated in our hospital were retrospectively analyzed, and the characteristics of disease, efficacy of chemotherapy and influencing factors for prognosis were explored, so as to provide a powerful basis for the treatment of such patients.

Methods

Objects of study

The clinical data of 89 children newly diagnosed with AML were collected. Inclusion criteria: 1) patients aged ≤16 years old at the time of initial diagnosis, 2) those who met the diagnostic criteria in the *Suggestion of Diagnosis and Treatment of Acute Myeloid Leukemia in Childhood* developed by the Subspecialty Group of Hematology, the Society of Pediatrics, Chinese Medical Association in November 2006, 3) those diagnosed based on morphological changes in bone marrow, and myeloblasts + promyelocytes (or monoblasts + promonocytes) ≥20% in bone marrow smears, besides clinical signs and symptoms and hemogram changes, 4) erythroid cells ≥50% with morphological abnormalities for acute erythroid leukemia (M6) besides the above criteria, and 5) megakaryoblasts ≥30% in bone marrow for acute megakaryoblastic leukemia (M7). Exclusion criteria: 1) patients who voluntarily abandoned the treatment not due to disease, 2) those undergoing HSCT not due to recurrence, or 3) those with APL. This study was approved by the Ethics Committee of the First Affiliated Hospital of Air Force Medical University. Signed written informed consents were obtained from all participants before the study entry.

According to the risk stratification based on cytogenetics and molecular biology in AML guidelines of the National Comprehensive Cancer Network (NCCN), the patients were divided into 3 clinical risk degrees [10]. Low risk: a good karyotype: t (8;21), inv (16) and t (9;11). Intermediate risk: the degree between low risk and high risk, no good karyotype, and leukemia cells <20% in the bone marrow smear examination after the first course of treatment. High risk: karyotype: -5, -7, t (6;9), leukemia cells >20% in the bone marrow smear examination after the first course of treatment, development of myelodysplastic syndrome into AML, and secondary AML. If there was no good karyotype, even patients who had a good prognosis (such as M4eo) suggested by morphological examination could not be included into the low-risk group.

Treatment methods

In low-risk group, the patients received the DAE remission induction and 1 course of MMA post-induction therapy. DAE regimen: daunorubicin (DNR), 40 mg/(m^2•d) on d 1, 3 and 5, cytarabine (Ara-C), 100 mg/m^2, q12 h on d 1-7, and etoposide (VP-16), 100 mg/(m^2•d) on d 1-5. MMA regimen: mitoxantrone (MIT), 8/10 mg/(m^2•d) on d 1-3, Ara-C, 1000 mg/m^2, q12 h on d 1-3. Then, 1 course of consolidation therapy was performed using 12 g of CLASP and HA regimen, respectively. CLASP regimen: Ara-C, 3000 mg/m^2, q12 h on d 1, 2 and 3 for a total of 4 or 6 doses, and L-asparaginase (L-ASP), 6000 U/m^2 for 1 dose, intramuscularly injected 3 h after the last dose of Ara-C. HA regimen: homoharringtonine (Har), 6 mg/(m^2•d) on d 1-5, and Ara-C, 50 mg/m^2, intramuscularly injected q12 h on d 1-5.

In intermediate- and high-risk groups, the patients received the DAE remission induction and 1 course of MMA post-induction therapy. Then, 2 courses of consolidation therapy were performed based on whether complete remission (CR) was achieved in the first course of DAE regimen. If CR was achieved after the first course of DAE regimen, 1 course of consolidation therapy was performed using 8 mg of MMA and 12 g of CLASP, respectively. If CR was achieved in the second course of DAE regimen, 1 course of consolidation therapy was performed using 10 mg of MMA and 18 g of CLASP, respectively.

In the case of central nervous system leukemia (CNSL), Ara-C/dexamethasone (Dex)/methotrexate (MTX) were intrathecally injected for 2-3 times during induction and consolidation therapy. Then they were intrathecally injected once every 2-3 months for 6-8 times in total. If CNSL occurred during the initial treatment, it was treated correspondingly. It is recommended that recurrent patients be treated with allogeneic HSCT (allo-HSCT).

Observation indexes

The bone marrow remission was preliminarily evaluated for all patients on 8 d after induction therapy, and the bone marrow examination on 28 d was the final criterion for the efficacy of remission induction. The evaluation criteria were as follows: CR: normal bone marrow hyperplasia, juvenile cells ≤5%. Partial remission (PR): normal bone marrow hyperplasia, juvenile cells = 6-19%. No remission (NR): juvenile cells ≥20%.

The adverse reactions of chemotherapy were evaluated according to the WHO evaluation criteria for acute and subacute toxicities of antitumor drugs. The recurrence and survival status of patients were recorded via follow-up till May 2020. Event-free survival (EFS) refers to the duration from diagnosis to event or deadline of follow-up, and overall survival (OS) refers to the duration from diagnosis to death or deadline of follow-up.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test or Fisher's exact probability test were performed for comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was performed. The influenc-

ing factors for the long-term survival were analyzed using univariate and multivariate Cox regression analyses. P<0.05 suggested statistically significant difference.

Results

General conditions of patients

A total of 89 children with newly-diagnosed AML met the inclusion criteria, and they had a median age of 4.14 years (0.9-15.1). The general conditions of patients and the characteristics of disease are shown in Table 1. Among them, there were 56 cases (62.9%) of fever, 50 cases (56.2%) of bleeding, 14 cases (15.7%) of bone pain, 71 cases (79.8%) of superficial lymphadenopathy, 22 cases (24.7%) of liver enlargement (≥5 cm below the costal margin in the right midclavicular line), and 12 cases (13.5%) of spleen enlargement (≥5 cm below the costal margin in the left midclavicular line). Extramedullary infiltration occurred in 34 cases (38.2%), including 13 cases of CNSL, 14 cases of pulmonary infiltration, 4 cases of chloroma, 1 case of mediastinal infiltration and 1 case of breast infiltration.

The chromosome karyotype and/or FISH test results were obtained in all of the 89 patients. The results were normal in 28 cases (31.5%), and abnormal in 61 cases (68.5%). Among the 61 cases, there were 19 cases with t (8; 21) and/or ETO-AML1^{+}, 3 cases with t (9; 11) and/or MLL gene rearrangement, 9 cases with inv (16) and/or CBFB gene rearrangement, and 30 cases with abnormalities of structure and number of other chromosomes, or 3 or more complex karyotypes.

Remission induction in patients

CR was achieved in 71 cases (79.8%) after the first course of treatment, 13 cases (14.6%) after the second course of treatment, and 5 cases (5.6%) after the third course of treatment.

Incidence of adverse reactions

During treatment, there were 21 cases of severe infection, including 9 cases of sepsis (1 case of Klebsiella pneumoniae, 3 cases of Escherichia coli, 3 cases of Pseudomonas aeruginosa, 1 case of Enterococcus faecium, and 1 case of Staphylococcus aureus), 8 cases of pulmonary infection, 3 cases of ileocecal infection and 1 case of bone marrow infection. Severe infection occurred in 7 cases during the induction stage 1, 6 cases during the consolidation stage 2, and 8 cases from the induction stage 2 to consolidation stage 1. Acute impairment of renal function was caused in 1 case due to ileocecal infection during the induction stage 1, so the chemotherapy was suspended, and the renal function was restored after infection control. In 1 case, chemotherapy was suspended due to bone marrow infection, and the symptom was improved after symptomatic treatment.

Recurrence and survival status of patients

As of October 31, 2019, a total of 23 cases (25.8%) had recurrence in the bone marrow. There were 3 cases of recurrence during chemotherapy, 12 cases of recurrence after chemotherapy and within 1 year after diagnosis, and 8 cases of recurrence after chemotherapy and within 2 years after diagnosis.

A total of 30 out of 89 patients died, of which 21 died of recurrence in bone marrow, 3 died of transplantation-related complications, and 6 died of severe infection during treatment. At the end of follow-up, the median follow-up time was 37.2 months, and the 5-year EFS rate and OS rate were 53.9% and 66.3%, respectively. The survival curves

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Cases (n=89) n (%)*
Gender (Male/Female)	54/35
Age (years)	4.14±4.34
Risk degree	
Low-risk	31 (34.8)
Middle-risk	36 (40.4)
High-risk	22 (24.7)
Extramedullary infiltration	
Yes	34 (38.2)
No	55 (61.8)
Karyotype	
Normal	28 (31.5)
t (8; 21)	19 (21.3)
inv (16)	9 (10.1)
t (9; 11)	3 (3.4)
-5	2 (2.2)
-7	1 (1.1)
Other abnormity	27 (30.3)
FAB type	
M0	1 (1.1)
M1	3 (3.4)
M2	25 (28.1)
M4	11 (12.4)
M5	32 (36.0)
M6	2 (2.2)
M7	10 (11.2)
Undifferentiated Type	5 (5.6)

FAB: French, American, British.

plotted by the Kaplan-Meier method are shown in Figure 1.

Based on the degree of risk, the children were divided into low-risk group (n=31), middle-risk group (n=36) and high-risk group (n=22). In the three groups, the 5-year OS rate was 74.2, 72.2 and 45.5%, respectively, without statistically significant differences (p=0.102), while the 5-year EFS rate was 67.7, 55.6 and 31.8%, respectively, with statistically significant differences (p=0.038) (Figure 2).

Allo-HSCT was performed in 5 cases (5.6%) after bone marrow remission in another hospital. Among them, 1 case died of transplantation-related complications, 2 cases achieved sustained remission, and 2 cases waited for transplantation.

Analysis of predictors affecting patient's survival

The gender, age, presence or absence of extramedullary infiltration, peripheral hemogram at initial diagnosis, immune phenotype cluster of differentiation (CD)56$^+$, serum lactate dehydrogenase (LDH), ferritin, chromosome karyotype and/or FISH test results, FAB type, and course of remission induction were included into the univariate analysis. The results showed that the long-term efficacy was poor in patients with extramedullary infiltration at the time of initial diagnosis and CD56$^+$, but it was better in patients who achieved CR after the first course (p=0.002, p<0.001, p=0.017). The gender, age, peripheral hemogram at initial diagnosis, serum LDH, ferritin, chromosome karyotype and/or FISH test results and FAB type had no obvious correlations with the 5-year EFS (p>0.05) (Table 2).

The presence or absence of extramedullary infiltration, immune phenotype CD56, CR achieved after the first course and recurrence time <1 year were included into the Cox proportional hazards model for multivariate analysis. It was confirmed that extramedullary infiltration at the time of initial diagnosis [HR=3.313 (95% CI: 1.748-13.664), p<0.001], CD56$^+$ [HR=1.592 (95% CI: 1.172-2.255), p=0.022] and recurrence time <1 year [HR=3.040 (95% CI: 1.087-5.508), p=0.018] were independent risk factors affecting the prognosis of patients, and CR achieved after the first course [HR=0.786 (95% CI: 0.228-0.803), p=0.036] was an independent factor improving the prognosis of patients (Table 3).

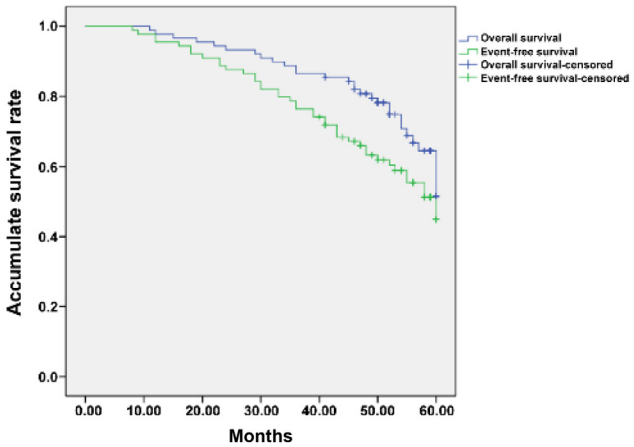

Figure 1. Kaplan-Meier survival curves of children with acute myeloid leukemia shown are the overall survival rate and event-free survival rate of children with acute myeloid leukemia (p<0.05).

Discussion

AML is a highly heterogeneous malignancy with a high recurrence rate and low OS and EFS rates. With the development of molecular biology in recent years, increasingly more prognosis-related cytogenetic factors, molecular biological factors (including fusion gene, somatic mutation and gene overexpression) and early treatment response fac-

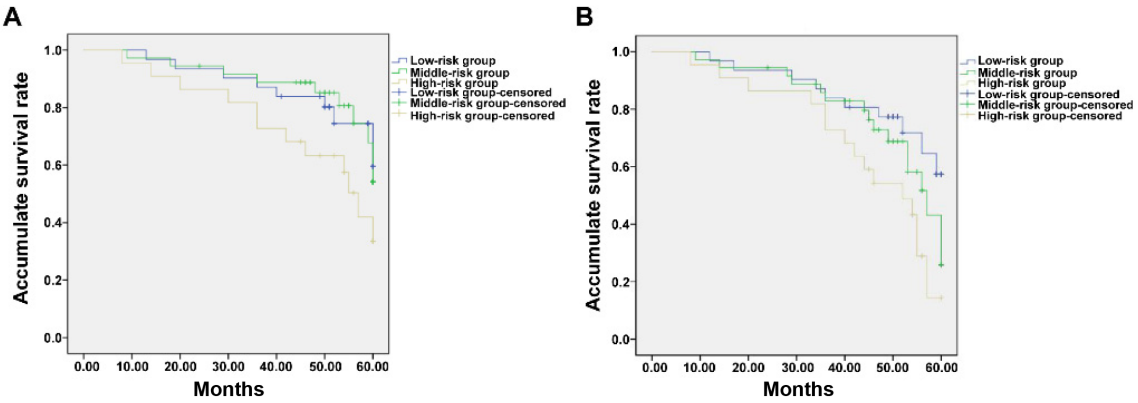

Figure 2. Kaplan-Meier survival curves of acute myeloid leukemia in children with different risk degrees. The difference between overall survival rate **(A)** of acute myeloid leukemia with different risk degrees had no statistical significance (p=0.102), while event-free survival rate **(B)** of acute myeloid leukemia with different risk degrees had statistical significance (p=0.038).

Table 2. Univariate analysis of predictors for 5-year event-free survival rate in children with AML

Parameters	*Cases (n=89) n (%)*	*5-year event-free survival rate (%)*	*p value*
Gender			0.668
Male	54 (60.7)	51.9	
Female	35 (39.3)	57.1	
Age (years)			0.665
<2	16 (18.0)	43.8	
2-10	39 (43.8)	56.4	
≥10	34 (38.2)	55.9	
Extramedullary infiltration			0.002
Yes	34 (38.2)	32.4	
No	55 (61.8)	67.3	
WBC ($\times 10^9$/L)			0.373
<50	59 (66.3)	57.6	
≥50	30 (33.7)	46.7	
Hemoglobin (g/L)			0.510
<90	57 (64.0)	50.9	
≥90	32 (36.0)	59.4	
Platelets ($\times 10^9$/L)			0.390
<50	38 (42.7)	47.4	
≥50	51 (57.3)	58.8	
LDH			0.833
<Triple	47 (52.8)	55.3	
≥Triple	42 (47.2)	52.4	
Ferritin			0.476
<Triple	66 (74.2)	51.5	
≥Triple	23 (25.8)	60.9	
Chromosome/ FISH			0.173
Normal	28 (31.5)	71.4	
t (8; 21)/ ETO-AML1	19 (21.3)	63.2	
inv (16)/ CBFB	9 (10.1)	55.6	
t (9; 11)/ MLL	3 (3.4)	66.7	
Others	30 (33.7)	30.0	
CD56			0.001
Positive	43 (48.3)	30.2	
Negative	46 (51.7)	76.1	
FAB type			0.083
M0	1 (1.1)	0	
M1	3 (3.4)	33.3	
M2	25 (28.1)	44.0	
M4	11 (12.4)	81.8	
M5	32 (36.0)	65.6	
M6	2 (2.2)	50.0	
M7	10 (11.2)	20.0	
Undifferentiated Type	5 (5.6)	60.0	
CR			0.017
1 course	71 (79.8)	60.6	
2 or more	18 (20.2)	27.8	

AML: Acute myeloid leukemia; WBC: White blood cell; LDH: Lactate dehydrogenase; FISH: Fluorescence in situ hybridization; FAB: French, American, British; CR: Complete remission

Table 3. Multivariate Cox regression analysis of predictors for AML in children

Parameters	*HR*	*95%CI*	*p value*
Extramedullary infiltration	3.313	1.748-13.664	0.001
CD56 (+)	1.592	1.172-2.255	0.022
CR achieved after 1 course	0.786	0.228-0.803	0.036
Recurrence <1 year	3.040	1.087-5.508	0.018

AML: Acute myeloid leukemia; CR: Complete remission; HR: Hazard ratio; CI: Confidence interval

tors (including bone marrow cytology evaluation and assessment of minimal residual disease after remission induction) have been recognized and applied to the risk stratification, based on which the stratified therapy is performed, improving the prognosis of children [11].

In this study, the survival status of patients was compared among different risk groups. The results revealed that there was no significant difference in the OS rate, but the EFS rate had statistically significant differences among the three groups, different from previous literature reports in foreign countries that both OS and EFS rates vary in different risk groups. For example, in the low-, intermediate- and high-risk patients receiving the Japanese AML-05 regimen, the 3-year OS rate was 93, 73 and 69%, and the EFS rate was 69, 57 and 53%, respectively [12]. In the low- and high-risk patients receiving the German AML-BFM 2004 regimen, the 5-year OS rate was 89 and 65%, and the EFS rate was 71% and 46%, respectively [13]. In the low-, intermediate- and high-risk patients receiving the American COG-AAML0531 regimen, the 3-year OS rate was 85, 69 and 48%, and the EFS rate was 71, 51 and 31%, respectively [14]. Moreover, in the low- and middle-risk patients receiving the British MRC-AML15 regimen, the 8-year OS rate was 95% and 63%, respectively [15]. The possible reason for such a difference is that the statistical analysis was biased due to the different criteria for risk stratification and limited sample size in our study.

In the present study it was found that the extramedullary infiltration at the time of initial diagnosis was an influencing factor for the prognosis of patients. The clearance rate of tumor cells is related to the prognosis of patients, and the children with extramedullary infiltration have a high load of leukemia cells and a slow clearance rate of tumor cells, so they can appropriately undergo enhanced remission induction and consolidation treatment, so as to improve the prognosis. In addition, studies have demonstrated that white blood cell (WBC) count at the time of initial diagnosis is an independent risk factor for the prognosis of AML, and patients with high peripheral WBC count often have a poor prognosis [16]. In this study, the 5-year EFS rate had no evident difference between children with WBC $\geq 50\times10^9$/L and those with WBC $<50\times10^9$/L, but it was still 10% lower in the former than in the latter, suggesting that the prognosis of children with high peripheral WBC count is worse.

It is currently believed that chromosome karyotype and genetic abnormalities of AML are independent prognostic factors. According to the NCCN risk stratification in 2010, t (8; 21) and inv (16) indicate good prognosis (low-risk group), while 11q23 except t (9; 11) indicates poor prognosis (high-risk group). In this study, the long-term survival rate was higher in children with t (8; 21)/ETO-AML1, inv (16)/CBFB and t (9; 11)/MLL gene inversion, while it was lower in patients with chromosome abnormalities, including 11q23/MLL gene rearrangement and complex karyotypes. Although such a difference was not significant, it was still more than 20%, basically consistent with the literature reports [17,18]. Besides, the efficacy was similar between children with t (8; 21)/ETO-AML1 and those with normal results, and there was no remarkable improvement in the long-term EFS rate, inconsistent with the fact that the long-term survival rate is higher in low-risk group according to the NCCN guidelines. The possible reason is that some cases have $CD56^+$, thus raising the recurrence rate. Therefore, whether the immune phenotype CD56 exists should be alerted in the grouping of children with t (8; 21)/ETO-AML1. In the case of $CD56^+$, the dose and duration of chemotherapy can be appropriately increased, which may help reduce recurrence.

Recurrence is a major problem in the treatment of leukemia. Children with recurrent AML have clear indications for transplantation. With the continuous optimization of risk stratification, especially the development of in-depth research based on cytogenetics and molecular biology, the overall therapeutic regimen has been revised by increasingly more children's blood centers. It is recommended that high-risk children undergo

transplantation after the first remission, such as AML-BFM2012. Transplantation is also recommended for CR1 children with high-risk factors and suspected recurrence [19,20]. Transplantation after recurrence can still achieve satisfactory efficacy and prolong survival.

This study is retrospective, in which the sample size was limited, the risk stratification was not accurate enough, the follow-up content was not comprehensive enough, and the influencing factors for CR after chemotherapy were not analyzed. In the future, the conclusion in this study needs to be confirmed by more rigorous large-sample prospective multicenter randomized studies.

Conclusions

The prognosis is poor in non-APL children with AML who have extramedullary infiltration at the time of initial diagnosis, $CD56^+$ and recurrence time <1 year, and CR achieved after the first course is an independent factor improving the prognosis of patients. The long-term EFS rate is significantly lower in high-risk group than that in low- and middle-risk groups. Intensive chemotherapy or early HSCT should be performed for high-risk patients.

Conflict of interests

The authors declare no conflict of interests.

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