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Clinical Characteristics and Prognosis of 27 Patients with Childhood Acute Megakaryoblastic Leukemia

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Background: The aim of this study was to investigate the clinical features and prognostic factors of childhood acute megakaryoblastic leukemia (AMKL).

Material/Methods: The data of 27 cases of childhood AMKL admitted from November 2009 to July 2018 were retrospectively analyzed. The survival analysis and prognostic factors were analyzed by Kaplan-Meier method.

Results: The median follow-up time was 26.4 months in 27 cases, and the complete response rate was 92.31% after 2 chemotherapy courses. Eight patients underwent bone marrow transplantation after 3–6 courses. Five patients died after transplantation, 4 of whom died due to recurrence after transplantation. Of the 27 patients, 10 developed recurrence (37.04%), and 8/10 had recurrence within 1 year. The 3-year overall survival rate and disease-free survival rates were (47±12)% and (36±14)%, respectively. Of the 27 AMKL cases, the 3 with Down syndrome (DS-AMKL) all survived after treatment, and the 3-year overall survival rate was 100%. However, of the other 24 AMKL patients without Down syndrome (non-DS-AMKL), 6 died and 6 abandoned treatment, and the 3-year overall survival rate was only 50%. Univariate analysis showed that 3-year overall survival rate was not correlated to gender, age, number of newly diagnosed white blood cells, karyotype, remission after 2 courses of treatment, and transplant after 3 courses of treatment of childhood AMKL cases. Nevertheless, recurrence and remission after 2 courses of treatment were significantly correlated with 3-year overall survival rate.

Conclusions: Children with non-DS-AMKL have a high degree of malignancy and are prone to early recurrence with a poor prognosis, whereas the prognosis of DS-AMKL is relatively good. Recurrence after treatment and remission after 2 courses of treatment are important factors influencing the prognosis of childhood AMKL. Recurrence after transplantation is the leading cause of death in transplantation patients.

MeSH Keywords: Hospitals, Pediatric • Leukemia, Megakaryoblastic, Acute • Prognosis

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Background

Acute megakaryoblastic leukemia (AMKL) is a subtype of acute myeloid leukemia (AML) characterized by abnormal megakaryocyte expressions of platelet-specific surface glycoproteins. Bone marrow biopsy often shows extensive myelofibrosis, which is characterized by dry tap [1]. AMKL is often associated with abnormal megakaryocyte proliferation, and megakaryocyte-specific antigens include CD41 (GPIIb/IIIa), CD42b (GPIb), CD61 (GPIIIa), and vwF (factor VIII) [2]. AMKL is extremely rare in adult AML, accounting for approximately 0.6% [3], while it is more common in childhood AML, accounting for 4–15% [4]. AMKL in non-Down syndrome patients (non-DS-AMKL) has often been associated with a poor prognosis, while children with Down syndrome (DS-AMKL) show a favorable outcome [5–7]. A multicenter clinical study showed that the 3-year survival rate of children with DS-AMKL was significantly higher than in non-DS-AMKL patients, and its chemotherapy intensity was lower [8]. *GATA1* mutations mostly occur in children with myeloid proliferations related to Down syndrome, and it can also occur in DS-AMKL, which may have a synergistic effect with chromosome 21 in developing myeloid proliferations [9]. A retrospective international study of 490 non-Down syndrome children with AMKL showed that patients with AMKL accounted for 7.8% of pediatric AML [8]. Their 5-year event-free (EFS) and overall survival (OS) were 43.7±2.7% and 49.0±2.7%, respectively [10]. Until the application of large-scale genome sequencing, the treatment of non-DS-AMKL patients was quite difficult due to the lack of reliable biological prognostic indicators [9]. A multicenter retrospective study of 153 children with AMKL showed the 4-year OS of the entire AMKL cohort was 56±4% and the 4-year EFS was 51±4% [11]. The study showed that pediatric AMKL with *RBM15-MKL1* had a 4-year OS of 70±11%, in contrast to the poorer outcomes in *NUP98-KDM5A, CBFA2T3-GLIS2, KMT2A*–rearranged patients (4-year OS 36±13%, 38±10%, and 33±13%, respectively) [12]. AMKL is a rare and refractory leukemia in children. The multicenter study populations in the above studies all came from European and American countries, while the subjects of our single center study were all Chinese, and 27 cases of AMKL were collected over 9 years. More importantly, our study shows that recurrence and remission after 2 courses of treatment are important factors influencing the prognosis of childhood AMKL, which has clinical value. De Rooij et al. performed RNA and exome sequencing on specimens from 99 patients and found that, except for *RBM15-MKL1, CBFA2T3-GLIS2, and KMT2A* gene rearrangements and *NUP98-KDM5A*, there was a new subtype of *HOX* gene rearrangement; patients with this new subtype had similar gene expression signatures and clinical outcomes [13]. Research on the genetic etiology of non-DS-AMKL rapidly led to a significant contribution in defining the prognosis. The present study retrospectively analyzed the clinical data and prognosis of 27 children with AMKL admitted to the Pediatric Department.

Material and Methods

Participants

Twenty-seven children with AMKL diagnosed in the Pediatrics Department from November 2009 to July 2018 were selected as subjects. The clinical information of the enrolled AMKL patients is shown in Table 1. The ID numbers (20, 24, 25) of 3 DS-AMKL patients are marked with * in Table 1. All patients were tested for related genes including *AML1-ETO, CBFB-MYH11, MLL-AF4, RBM15-MKL1, NUP98-KDM5A, CBFA2T3-GLIS2, KMT2A, WT1, FLT3, and GATA1*. No *GATA1* mutations were found in the 3 DS-AMKL patients. Inclusion criteria were: 1) 0 to 14 years of age; 2) All patients were diagnosed as AMKL by morphology, immunology, genetics, and molecular biology (MICM), and the diagnostic standards were in accordance with FAB (French-American-British) criteria [14]; and 3) Children with initial onset did not receive any previous leukemia-related treatment.

The enrolled patients were divided into groups according to sex, age, number of white blood cells, karyotype, remission after 2 courses of treatment, and transplantation after 3 courses of treatment. This research was approved by the Ethics Committee of the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University. Informed consent was obtained from the children's guardians.

Treatment

All children were treated with the SCMC-AML-2009 chemotherapy program from Shanghai Children's Medical Center hospital. Induction of remission therapy was: 1) DAE protocol: daunorubicin (DNR) 40 mg/(m^2·d)×3 d, cytarabine (Ara-c) 200 mg/(m^2·d)×7 d, etoposide (VP16)100 mg/(m^2·d)×3 d; 2) the MAE protocol was: mitoxantrone (MTZ) 10 mg/(m^2·d)×3 d, cytarabine (Ara-c) 200 mg/(m^2·d)×7 d, etoposide (VP16) 100 mg/(m^2·d)×3 d.

Consolidation and intensive treatment consisted of sequential use of the following 4 programs for 12 to 18 months and follow-up was performed after consolidation chemotherapy was completed: 1) hAD protocol: cytarabine (Ara-c) 3000 mg/(m^2·q12h)×3 d, daunorubicin (DNR) 40 mg/(m^2·d)×2 d; 2) hAE protocol: cytarabine (Ara-c) 3000 mg/(m^2·q12h)×3 d, etoposide (VP16) 100 mg/(m^2·d)×2 d; 3) hAM protocol: cytarabine (Ara-c) 3000 mg/(m^2·q12h)×3 d; mitoxantrone (MTZ) 10 mg/(m^2·d)×2 d; 4) AT protocol: cytarabine (Ara-c) 150 mg/(m^2·d)×7 d; 6-mercaptopurine (6-TG) 75 mg/(m^2·qn)×9 d.

Prevention and treatment of central nervous system leukemia consisted of a total of 4 to 6 triple intrathecal injections (including methotrexate, cytarabine, and dexamethasone).

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Table 1. Individual characteristics of the 27 AMKL patients.

ID	Age (month)	Gender	WBC, $\times 10^9$/L	Karyotype	Fusion gene	Treatment situation	CR	Relapse	Status
1	15.6	M	12.3	47, XY,+3	Negative	Recurrence after 8 treatments	Yes	Yes	Dead
2	7.8	F	4.4	53,XX,+der2,der5,+der6,+7,+8, +10,-13,+14,+19,+19/52,idem,-21	Negative	Follow-up after 10 treatments	Yes	No	Survival
3	13.4	M	13.6	Not available	Negative	Recurrence after 5 treatments	Yes	Yes	Abandoned
4	12.8	M	4.9	46, XY	Negative	Follow-up after 10 treatments	Yes	No	Survival
5	24.2	M	10.3	46,XY,t(3;11)(q12;p15),del(13) q12q14)/45,idem,der(10;15) (p10;p10),del(q11.2;q21),-del(15) (q11.2;q21)	Negative	Recurrence after 6 treatments	Yes	Yes	Abandoned
6	12.1	F	9.9	47,X,add(x)(q28)der(2) t(2;5)(p13;p13),del(6) (q13);der(7)t(1;7)(q10;q10) deo(8)(q21q24),del(11) (q13q21),add(13)(q32),der(16) t(6;16)(q22;p13.3),add(22)(q13). mar[14]/46,XX[6]	Negative	Give up after 1 treatment	No	No	Abandoned
7	15.4	M	8.3	46,XY,t(1;7)(q21;q36),del(6) (q21q25)	Negative	Secondary tumor M5 after 9 treatments	Yes	Yes	Abandoned
8	7.9	F	50.8	45,XX,t(2;4)(q33;q25),-14,+add(16)(p13)	Negative	Follow-up after 10 treatments	Yes	No	Survival
9	15.0	M	13.7	49,XY,del(4)(q31),+6,der(7)t(7;4) (q21;p21),+10,add(13)(p13)	Negative	Transplant after 3 treatments	Yes	No	Dead
10	7.9	M	12.1	48,XY,t(2;7)(p21;p15),+4,+19[20]	Negative	Follow-up after 10 treatments	Yes	No	Survival
11	26.7	M	12.8	46,XY,t(3,16)(p21;24)[20]	Negative	Follow-up after 10 treatments	Yes	Yes	Dead
12	43.7	M	8.9	Not available	Negative	Transplant after 4 treatments	No	Yes	Dead
13	18.1	F	5.9	46, XX	Negative	Transplant after 6 treatments	Yes	No	Survival
14	10.3	M	23.7	46, XY,t(4;12)(q25;p13)	Negative	Follow-up after 10 treatments	Yes	No	Survival
15	12.3	M	12.9	46, XY	Negative	Follow-up after 10 treatments	Yes	Yes	Abandoned
16	24.6	F	7.3	47, xx, add(6)(q27)+10[14]/46, xx[6]	Negative	Follow-up after 10 treatments	Yes	No	Survival
17	20.4	F	7.38	46, XY	Negative	Transplant after 3 treatments	Yes	Yes	Dead
18	5.1	M	7.3	46,XY,t(1;22)(p13;q13) [3]/46,XY[6]	*RBM15-MKL1*	Follow-up after 10 treatments	Yes	No	Survival
19	16.5	F	6.1	47,XX,+3,t(11,16,17) (q13;q24;q21)46,XX[15]	Negative	Transplant after 5 treatments	Yes	Yes	Dead

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Table 1 continued. Individual characteristics of the 27 AMKL patients.

ID	Age (month)	Gender	WBC, $\times 10^9$/L	Karyotype	Fusion gene	Treatment situation	CR	Relapse	Status
20*	16.3	F	60.01	54-56,xy,+x,add(1)(q44),+2,+6,+8,der(8)t(8)t(q21;p21),+10,+13,+19,+21,+22[cp20]	Negative	Follow-up after 10 treatments	Yes	No	Survival
21	12.5	F	4.4	46,xx,der(2)t(2;7)(p25;q11.1),del(7)(q11.2),der(10)dup(10)(p12p15)trp(10)(q24q26)inv(10)(q11.2q24)[12]/48,idem,+8,+mar[8]	Negative	Transfer to other hospital after 4 treatments	No	No	Survival
22	20.8	F	3.1	Not available	Negative	Follow-up after 6 treatments	Yes	No	Survival
23	22.2	M	15.3	46,XY	Negative	Recurrence after 5 treatments	Yes	Yes	Abandoned
24*	16.0	F	10.56	60,XX,+2,+6,+7,+der(8)t(1;8)(q24;p23),+del(11)(q21q23),+14,+14,+15,+19,+21,+der(21)t(13;21)(q14;q22),+22[20]	Negative	Transplant after 4 treatments	Yes	No	Survival
25*	5.0	F	15.72	47,XX,t(7;12)(p12;q24.1),+21[12]/46,XX[8]	*CBFA2T3-GLIS2*	Transplant after 4 treatments	Yes	No	Survival
26	66.8	M	12.55	46, XY	*CBFA2T3-GLIS2*	Transplant after 4 treatments	Yes	No	Survival
27	29.3	M	8.39	45, XY,-19,add(21)(p13)	Negative	Follow-up and stop drug after 6 treatments	Yes	No	Survival

* Three DS-AMKL patients

For hematopoietic stem cell transplantation, 8 patients with high-risk factors were given 3 to 6 chemotherapy courses, and allogeneic hematopoietic stem cell transplantation was performed after complete bone marrow remission. One of the 8 cases was converted to AMKL from MDS, 2 cases were positive for *CBFA2T3-GLIS2* fusion gene, 1 case had skull infiltration and the bone marrow immature cells were still greater than 15% after 1 course of chemotherapy, and the remaining 4 cases were bone marrow recurrence.

AMKL patients combined with Down syndrome were treated with a reduced-intensity European and American DS-AMKL treatment plan (Treatment of Children with Down Syndrome and Acute Myeloid Leukemia, Myelodysplastic Syndrome and Transient Myeloproliferative Disorder: A Phase III Group-Wide Study).

Bone marrow examination and clinical evaluation

Bone marrow puncture examination was performed after 2 rounds of induction chemotherapy and before consolidation chemotherapy. The examination included the original cell morphology, the proportion of immature cells, fusion gene, and the monitoring of minimal residual disease (MRD) by flow cytometry. The proportion of primitive and naive cells was <5% for M1 bone marrow, 5% to 25% for M2 bone marrow, and >25% for M3 bone marrow. MRD monitoring was performed using the monoclonal antibody combination group as a marker to screen for tumor cell immunophenotypes, with a sensitivity of 10^{-4}. MRD <0.01% was defined as negative, and MRD >0.01% was positive. Complete remission (CR) was defined as M1 bone marrow, and recurrence was defined as M2 or M3 bone marrow or extramedullary recurrence. Overall survival (OS) was recorded as the time from the date of initial diagnosis to death or end of follow-up, and event-free survival (EFS) was the duration from the initial diagnosis to the first event (recurrence, death, or end of follow-up).

Statistical analysis

Data analysis was performed using Statistical Product and Service Solutions (SPSS) 22.0 (IBM, Armonk, NY, USA). The chi-square test was used for comparing classification data and the *t* test was used for comparing measurement data. Comparison

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of survival rates and univariate analysis of prognosis were performed using the Kaplan-Meier method. Cases with a status of "abandoned" were counted as events. All measurement data are expressed as mean±SD. $p<0.05$ suggested that the difference was statistically significant.

Results

General information

Of the enrolled 27 patients, 15 were boys and 12 were girls. The male-to-female ratio was 1.25: 1, with an average age of 18.4 months and a median age of 15.6 months (5–66.8 months). Primary AMKL was found in 26 cases, and another secondary case was developed from MDS. Among the initial symptoms, 13 cases (48.1%) had anemia, 17 (63.0%) had hemorrhage, 12 (44.4%) had fever, 20 (74.1%) had hepatic enlargement, 18 (66.7%) had splenomegaly, and 1 (3.7%) had joint pain. At the beginning of the MRI examination, 3 cases of children had infiltration of the skull and surrounding soft tissue, 1 had appendix occupying the body with multiple bone destruction, 1 had knee joint bone disease, and 1 had thoracolumbar vertebral compression. In the early stage of the disease, the peripheral blood leukocyte count (WBC) was 13.43±12.94 (3.10–60.01)×10^9/L, the proportion of peripheral blood immature cells was 20.37±22.01% (0–67%), hemoglobin (Hb) was 78.15±20.51 (42 to 108) g/L, and the platelet (PLT) count was 46.37±67.17 (5–312)×10^9/L.

Bone marrow examination

The proportion of immature cells in the bone marrow of 27 patients before treatment were more than 20%, with an average of 67.4% (28.8–98.0%). The positive expressions of markers of leukemia immunoassay in all children were as follows: CD41-positive in 26 cases (96.3%), CD61-positive in 19 cases (70.4%), CD33-positive in 24 cases (88.9%), CD34-positive in 16 cases (59.3%), CD36-positive in 14 cases (51.9%), CD13-positive in 6 cases (22.2%), CD14-positive in 5 cases (18.5%), CD15-positive in 5 cases (18.5%), CD56-positive in 14 cases (51.9%), CD117-positive in 23 cases (85.2%), and HLA-DR-positive in 13 cases (48.1%).

Of the 27 patients, karyotype analysis was not conducted in 3 cases – 1 case did not have enough metaphase to analyze and 2 lacked enough bone marrow specimens due to dry pumping – and the remaining 24 patients underwent chromosome examination. Among the 24 cases, there were 6 cases (25%) with normal karyotype, 2 (8.3%) with hypodiploid containing 45 chromosomes, 6 (25%) with pseudo-diploid, 7 (29.17%) with hyperdiploid containing 47–50 chromosomes, and 3 (12.5%) with hyperdiploids containing over 50 chromosomes. There were 11 (45.8%) patients with complex karyotypes (more than 3 abnormal chromosomes), 3 (12.5%) had 21 trisomy (+21) karyotype, and 1 (4.2%) carried the t(1;22) anomalous chromosome. Fusion gene tests were performed in 27 patients; 1 patient was positive for *RBM15-MKL1*, 2 were positive for *CBFA2T3-GLIS2*, and the others were negative.

Efficacy assessment and follow-up of prognosis

One of the 27 patients discontinued treatment after the first course of chemotherapy, and the remaining 26 patients completed the induction chemotherapy. After 2 courses, 24 patients achieved CR, and the CR rate was 92.31%. Eight patients with high-risk factors underwent bone marrow transplantation after 3–6 cycles of chemotherapy. The clinical characteristics of 8 transplant patients are shown in Table 2. Five patients (62.5%) died during the follow-up period; 1 patient died of CMV pneumonia combined with intestinal GVHD after transplantation, and the other 4 patients (80%) died of recurrence after transplantation. The remaining 3 patients (37.5%) survived after transplantation. If a non-DS-AMKL (not DS-AMKL) patient converted from MDS disease, they were listed for transplantation (such as case 13). Case 24 with DS-AMKL was given a transplant because her chromosome was a complex karyotype. Case 25 with DS-AMKL had a transplant because she carried the *CBFA2T3-GLIS2* fusion gene.

The median follow-up time was 26.4 (1.6-85.3) months in 27 patients. None of them were lost to follow-up. In particular, 15 (55.6%) cases survived, 6 (22.2%) died, and 6 (22.2%) were abandoned. The ID numbers of the 6 abandoned cases were 3, 5, 6, 7, 15, and 23. Four of the 6 cases discontinued treatment because of recurrence during or after chemotherapy. Another case was due to no CR after the first chemotherapy. The last case was abandoned because of developing a second tumor at M5 after 9 chemotherapy courses. Their final outcomes were all deaths. Fourteen of the children who completed the chemotherapy course or bone marrow transplant achieved sustained remission, and the sustained remission rate was 51.9%. During the follow-up period, 10 patients relapsed (37.04%), 8 (80%) of whom relapsed within 1 year. The median time of recurrence was 8.1 (4.73–24.74) months. The median overall survival and event-free survival in 27 patients were 44.2 months and 32.2 months, respectively. The rates of 3-year overall survival (OS) and 3-year event-free survival (EFS) were (47±12)% and (36±14)%, respectively. The statistical results were shown in Figure 1.

Prognostic factor analysis

Univariate analysis results showed that recurrence ($p=0.001$) and bone marrow remission after 2 courses of chemotherapy ($p<0.001$) were significantly correlated with 3-year OS.

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Table 2. Individual characteristics of the 8 AMKL patients with transplantation.

ID	Age (month)	Karyotype	Fusion gene	CR before transplantation	MRD before transplantation	Relapse after transplantation	Status
9	15.0	49,XY,del(4)(q31),+6,der(7)t(7;4)(q21;p21),+10,add(13)(p13)	Negative	Yes	Negative	No	Dead (due to CMV pneumonia and intestinal GVHD)
12	43.7	Not available	Negative	No	Positive	Yes	Dead
13	18.1	46,XX	Negative	Yes	Negative	No	Survival (suspected conversion from MDS to AMKL)
17	20.4	46,XY	Negative	Yes	Positive	Yes	Dead
19	16.5	47,XX,+3,t(11,16,17)(q13;q24;q21)46,XX[15]	Negative	Yes	Positive	Yes	Dead
24	16.0	60,XX,+2,+6,+7,+der(8)t(1;8)(q24;p23),+del(11)(q21q23),+14,+14,+15,+19,+21,+der(21)t(13;21)(q14;q22),+22[20]	Negative	Yes	Negative	No	Survival (conversion from MDS to AMKL)
25	5.0	47,XX,t(7;12)(p12;q24.1),+21[12]/46,XX[8]	*CBFA2T3-GLIS2*	Yes	Negative	No	Survival
26	66.8	46, XY	*CBFA2T3-GLIS2*	Yes	Negative	No	Survival

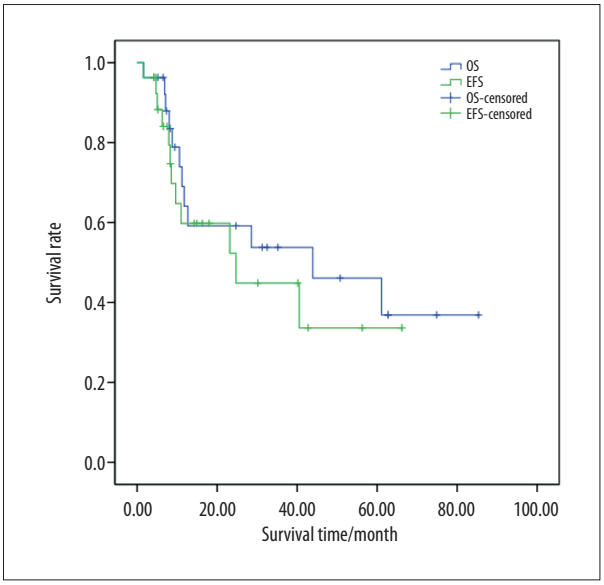

Figure 1. Survival curve of 27 children.

The long-term survival time of children with recurrence was obviously lower than that of children who had not relapsed. Similarly, the long-term survival rate of children who did not relapse after 2 courses of chemotherapy was also clearly lower than that of children who relapsed. Sex, age, initial white blood cell count, complex karyotypes of chromosome, and transplantation after 3 courses of treatment were not correlated with OS ($p>0.05$). The statistical results are shown in Table 3.

Discussion

Acute megakaryoblastic leukemia (AMKL) in children can be divided into 2 subgroups: AMKL with Down syndrome (DS-AMKL) and AMKL without Down syndrome (non-DS-AMKL). It is the most common type of leukemia that is predisposed to children with Down syndrome [15]. AMKL is a heterogeneous disease with a high incidence of complex karyotypes. Many children carry fusion genes, including *RBM15-MKL1, CBFA2T3-GLIS2, NUP98-KDM5A*, and *HOX* gene rearrangements [16,17]. The most common cytogenetic abnormality in children with non-DS-AMKL is t(1;22)(p13;q13), leading *RMB15* gene on chromosome 1 and *MLK1* gene on chromosome 22 to form the *RBM15-MKL1* fusion gene [18]. Of the 27 children with AMKL in this study, only 6 (25%) had normal karyotypes, 11 (45.8%) had complex karyotypes, 1 carried positive *RBM15-MKL1* gene, 2 carried positive *CBFA2T3-GLIS2* gene, 1 carried positive *MLL* gene, and 3 had Down syndrome.

The overall prognosis of AMKL is poor, except for children with Down syndrome, who have a better prognosis. Even active application of an intense chemotherapy series fails to present

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Table 3. Univariate analysis of long-term survival.

Prognostic factors	Number of cases	3-year OS (%)	χ^2	P value
Gender				
Male	15	30.3±6.6	1.104	0.314
Female	12	57.4±11.3		
Age				
<1 years old	6	71.5±11.2	3.229	0.072
≥1 years old	21	31.1±6.4		
WBC				
$\geq 10\times10^9$/L	14	33.6±8.7	0.733	0.392
$<10\times10^9$/L	13	52.9±11.1		
Karyotype				
Complicated	11	48.5±13.5	0.008	0.930
Uncomplicated	14	40.3±6.7		
Relapse				
Yes	17	14.6±3.1	10.412	0.001
No	10	65.5±8.3		
Bone marrow status after 2 treatments				
CR	25	47.4±7.8	12.500	<0.001
No CR	2	3.4±1.3		
Transplantation after 3 treatments				
Yes	8	24.9±10.3	2.532	0.112
No	19	53.1±9.2		

OS – overall survival; WBC – blood leukocyte count; CR – complete remission.

a satisfactory prognosis of AMKL, and its disease-free survival rate and overall survival rate are lower than in other types of acute myeloid leukemia [19]. The chemotherapy CR rate of AMKL is similar to other AML subtypes, but its overall median survival time is only 18–40 weeks [20]. Recent studies have reported that DS-AMKL has a good prognosis [21] while non-DS-AMKL has a relatively poor prognosis [22].

There were 3 DS-AMKL patients (ID numbers 20, 24, and 25) in the 27 AMKL cases. The patient with ID number 20 survived after completing 10 chemotherapy courses. Another patient with ID number 24 had a complex karyotype; after 4 chemotherapy courses, she underwent bone marrow transplantation and survived. The patient with ID number 25 carried the *CBFA2T3-GLIS2* fusion gene; after 4 chemotherapy courses, she underwent bone marrow transplantation and survived. Three cases with Down syndrome (DS-AMKL) all survived after treatment, and the 3-year overall survival rate was 100%. However, of the other 24 AMKL patients without Down syndrome (non-DS-AMKL), 6 died and 6 abandoned treatment, and the 3-year overall survival rate was only 50%. Transient abnormal myelopoiesis (TAM) is transient proliferation of immature megakaryocytes and occurs in 5–10% of perinatal infants with Down syndrome [23]. TAM is self-limiting in most cases and usually terminates spontaneously within 3–4 months after birth [23]. The myeloid neoplasms of Down syndrome have a similar behavior that is independent of blast cell count, and these are not subclassified into MDS or AML. Both TAM and myeloid leukemia associated with Down syndrome are characterized by *GATA1* mutations and mutations of the *JAK-STAT* pathway, with additional mutations identified in the myeloid leukemia cases [24]. The additional mutations include multiple adhesion protein components, *CTCF, EZH2, KANSL1* and other epigenetic regulatory factors, as well as common signaling pathways, such as *JAK* family kinases, *MPL, SH2B3* and multiple *RAS* pathway genes [24]. Recent studies have shown that children with non-DS-AMKL with t(1;22) have a better prognosis than other non-DS-AMKL patients [25]. For instance, 6 of 11 non-DS-AMKL patients with t(1;22) are survived for long periods of time in a clinical study, while patients with other

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types of non-DS-AMKL died [26]. Only 1 patient with t(1;22) in our study was followed up after completing 10 chemotherapy courses, the patient survived for 31.31 months and was in a state of continuous remission, suggesting a good prognosis. *CBFA2T3-GLIS2* is a common fusion gene of AMKL, and testing positive for this gene often indicates a poor prognosis [27]. In this study, there were 2 patients with positive *CBFA2T3-GLIS2*, and 1 patient underwent bone marrow transplantation after 2 chemotherapies (MRD was negative after one chemotherapy). Another patient received a bone marrow transplantation after 4 chemotherapies (MRD was negative after 3 chemotherapies). The 2 patients survived to the follow-up date, and the long-term prognosis needs further follow-up.

The European Bone Marrow Transplantation Group retrospectively analyzed the recurrence rates of total autologous transplantation and allogeneic bone marrow transplantation in children and adults, which are 82% and 43%, respectively [28]. These 2 therapies are associated with higher recurrence rates. Autologous transplantation is not recommended as a treatment option owing to its poor long-term efficacy. Although allogeneic transplantation also has a higher recurrence rate, it is the best choice for patients with non-DS-AMKL after remission, and its efficacy is better than that of conventional chemotherapy [28]. The treatment-related mortality rate of AMKL children with bone marrow transplantation is relatively low, while the rate in adults is relatively high, at 26% [28]. Eight patients in this study underwent bone marrow transplantation after remission, and 5 deaths occurred during follow-up. Only 1 of them died of CMV pneumonia combined with intestinal GVHD after transplantation, which was considered as a transplant-related death. The remaining 4 patients all died of recurrence after transplantation (the recurrence rate was 50%), which was similar to some previous reports [29]. The research subjects in the above studies were white, while our subjects were Asian (Chinese). In addition, we discovered that recurrence and remission after 2 courses of treatment are key factors influencing the prognosis of childhood AMKL. We also described specific treatment strategies and summarized some of the high-risk factors of transplantation. Our general treatment principle is to give chemotherapy first, and then decide whether to transplant. This is based on the response to chemotherapy and other high-risk factors. Non-DS-AMKL has the indication for transplantation if it has any of the following conditions: a) MDS-transformed AML; b) Complex karyotypes and secondary tumors; c) Reexamination of bone marrow after 1 course of induction therapy revealed naive cells >15%; d) After 2 chemotherapy treatments, 2 examinations of the bone marrow minimal residual lesions all revealed MRD >1%.

The CR rate of AMKL is comparable to that of other subtypes of AML. However, both chemotherapy and bone marrow transplantation have a high recurrence rate. Its low overall survival rate indicates that AMKL requires new therapies. The improvement in overall survival will not come from the improvement of traditional chemotherapy methods, but rather from molecular targeted therapy for macrophage differentiation and breakthroughs in combating chemoresistance against chemotherapy [29]. Normal megakaryocytes can leap over terminal mitosis into polyploidy, whereas leukemia megakaryocytes cannot undergo terminal polyploidization [30]. Assuming that a polyploid inducer can promote normal terminal differentiation of leukemia cells, it can be used in AMKL treatment. A recent study by Wen et al. determined that Aurora kinase A (AURKA) is a polyploid-negative regulator that can serve as a potential drug target for inducing polyploidization. They further found that MLN8237 is a selective genomic inhibitor of AURKA kinase, which induces multiplication and thus exerts potent anti-AMKL activity and is clinically promising [31]. RUNX1 is important in normal hematopoiesis and it is upregulated in megakaryocytes of DS-AMKL [32]. Overexpression of RUNX1 enhances chemoresistance in chemotherapy, and reverse experiments demonstrated that knockdown of RUNX1 increases chemotherapeutic sensitivity of cytarabine [33]. It is suggested that RUNX1 or its downstream genes can be used as a molecular target to provide a new potential treatment for AMKL.

Conclusions

In summary, AMKL is a malignant hematological disease with poor prognosis, which is often accompanied by karyotypic abnormalities. Chemotherapy and bone marrow transplantation are currently the main treatment methods, but they all have high recurrence rates and we need to develop new therapies to improve the prognosis. Due to the low incidence of this disease and the limited clinical sample capacity, some conclusions may be biased. Multicenter large-scale clinical research is needed to better understand AMKL.

Conflict of interest

None.

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