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Analysis of prognostic factors in children with acute lymphoblastic leukemia

Linlin Li

Department of Pediatric, Qingdao University, Qingdao, 266071 China

Abstract: **Explore the related factors affecting the prognosis of children with acute lymphoblastic leukemia. Clinical data of 48 newly diagnosed children were collected with ALL in the Yantai Yuhuangding Hospital from Janurary 2016 to December 2018. Statistics of the children's gender, age, immunophenotype, abnormal chromosome karyotype and fusion gene screening and other indicators were analyzed the relationship with prognosis. There were 48 children diagnosed acute lymphoblastic leukemia, 31 boys and 17 girls, the average age is 5.2 years. There were 45 cases of B-ALL, 3 cases of T-ALL. 30 cases were normal for chromosome karyotype, 18 cases were abnormal. 12 cases were positive for fusion gene: TEL/AML1 5cases, MLL/AF4 2cases, E2A/PBX1 3cases, MLL/AF9 1case and FLT3-ITD 1 case. Of all the patients, 6 cases died, among them, 1 case was without abnormal chromosome karyotype and fusion gene, 2 cases were both of abnormal chromosome karyotype and fusion gene, 2 cases were abnormal chromosome karyotype and fusion gene in once case. Detection of age, sex, immunophenotype, chromosome karyotype and fusion genes is essential for the prognosis of childhood acute lymphoblastic leukemia.**

Keywords: Acute Lymphoblastic Leukemia; Immunophenotype; Chromosome karyotype; Fusion genes

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*Corresponding Author: Linlin Li, 498600462@qq.com

1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignant tumor with abnormal proliferation of a large number of primitive and naive lymphocytes in the bone marrow. With the development and application of cytomorphology, immunology, cytogenetics, molecular biology and gene sequencing, it provides a basis for the effective evaluation and precise treatment of all in children. Now the total 5-year survival rate of all is up to 90%[1]. However, there are still some children with relapse, bone marrow suppression and infection in the course of chemotherapy, and finally death due to treatment failure. Children's age at onset, gender, immunophenotypy, chromosome karyotype, and fusion genes play an important role in evaluating the prognosis of children[2,3]. This study reviewed the children of ALL admitted to the Affiliated Yantai Yuhuangding Hospital of Qingdao University. We analyzed the age, sex, immunophenotype, chromosome karyotype and fusion genes, and explored their impact on the prognosis of children with ALL.

2. Materials and Methods

2.1. Research object

To collect clinical data of newly diagnosed ALL children with bone marrow cell morphology, immunotyping, cytogenetics, molecular biology, etc. from 2016 to 2018 and treated according to the CCCG-ALL-2015 protocol in the Affiliated Yantai Yuhuangding Hospital of Qingdao University. A total of 48 cases were collected, aged 1.3 to 12.6 years, with an average age of 5.2 years, including 31 boys and 17 girls.

2.2. Methods

Forty-eight children with ALL were retrospectively analyzed and statistically compared with sex, age, leukemia immunophenotyping, karyotype and gene mutation.

2.3. Clinical follow-up

All the cases were followed up the child by hospitalization, outpatient clinic, telephone and end point was June 2019.

2.4. Statistical analysis

SPSS21.0 statistical software was used for statistical analysis. Count data was chi-square test. Due to sample size, Fisher's exact probability method and continuity-corrected chi-square test were used. Measurement data were expressed as mean ± standard deviation( ) . The homogeneity of variance data was tested by t test, and $P \leqslant 0.05$ was considered statistically significant.

3. Results

3.1. Relationship between age, sex and prognosis of children

A total of 48 cases of ALL children with clinical data were collected, including 31 boys (64.6%) and 17 girls (35.4%). The 6 children who died were all boys. Statistical analysis showed no significant difference (P> 0.05). Details are shown in Table 1. Forty-eight children were 1.3 to 12.6 years old, with an average age of 5.2 years. Statistical analysis showed that No difference (P> 0.05), see Table 2.

Table 1. Correlation analysis of gender and prognosis

prognosis	gender		P value
	boy	girl	
death	6	0	0.077
survival	25	17	

Table 2. Correlation analysis of age and prognosis

prognosis	age	T value	P value
death	7.72±4.68	-1.75	0.086
survival	4.93±3.50		

3.2. Statistics of chromosome karyotype and fusion genes

Of the 48 children with ALL, 45 were B-ALL (93.75%) and 3 were T-ALL (6.25%). There were 30 cases (62.5%) with normal chromosome karyotype and 18 cases (37.5%) with abnormality, including 6 cases (12.5%) with hyperdiploid. 12 cases of fusion gene were positive cases. The abnormal chromosome karyotype and/or fusion genes were shown in Table 3 below.

Table 3. The abnormal chromosome karyotype and/or fusion genes

Serial number	abnormal chromosome karyotype	fusion genes
1	47,xy,?+10[1]/47,xy,?+10,12p-[1]/46,xy[10]	TEL/AML1
2	46,xx	TEL/AML1
3	42/45,xy[cp5]	MLL-AF4
4	45,xy,-11,-12,+mar[10]/46,xy[2]	-
5	54-62,xx,+x,+4,+6,+6,+8,+10,+11,+12,+13,+14,+15,+18,+20,+22,+mar,inc[cp8]/46,xx,[2]	-
6	46,xy,t(3,9)[7]/46,xy,[1]	-
7	46,xy[15]	TEL/AML1
8	46,xy,?t(5;12),?7q-,?der(11),?14q+[5]/46,xy[18]	-
9	46,xy,t(12;22)[2]/46,xy[12]	-
10	56,xx,+x,+3,+6,+8,+10,?t(12;18),+14,+18,+18,+18,+21,+21[20]	-
11	60,xy,+x,+y,+6,+8,+9q+,+11,+14*2,+17,+18,+21,+1-2mar,inc[cp6]/46,xy[12]	-
12	46,xy,3p-,t(12,13)?[9]/46,xy[13]	E2A/PBX1
13	46,xy	TEL/AML1
14	47,xy,+5[6]/46,xy[5]	-
15	46,xy	TEL/AML1
16	54-55,xy,+x,+y,+6,+10,+14,+17,+19,+21,+mar,inc[cp4]/46,xy[7]	-
17	46,xy,9p-,t(9;22)[11]	-
18	53,xx,+x,+4,+6,+14,+17,+18,+21[4]/46,xx,[9]	-
19	45-47,xy,der(9),-12,-12,13p+,ph,+ph,+mar2[cp5]/46,xy[1]	-
20	46,xy,inv(9)(p12;q13)[20]	-
21	46,xy[20]	E2A/PBX1
22	46,xy[20]	MLL-AF4

23	46,xx[10]	E2A/PBX1
24	61,xxy,-1,-2,-7,-10,-17,-19,-20[1]/46,xy[10]	FLT3-ITD
25	46,XY[20]	MLL-AF9
26	46,?xq-,?der(x),3q-,-4,-10,+?2mar,inc[cp2]/46,xx[15]	-

3.3. The relationship between Immunophenotype, chromosome karyotype, fusion genes and prognosis in children

There were 6 deaths (12.5%) among 48 children with ALL. Immunotyping and chromosome karyotype were the factors that affect the prognosis (P <0.05), and the fusion gene had no relation to the prognosis (P> 0.05). See Table 4-6 for details.

4. Discussion

Acute lymphoblastic leukemia is the most common malignant tumor of the lymphatic hematopoietic system in childhood. With the continuous improvement of the diagnosis and treatment level, the long-term survival rate of children has improved significantly. At present, the 5-year EFS can be as high as 90%, but after the initial remission, still 15-20% recurrence rate[4]. Our statistical results showed that the survival rate was 87.5%, but some children were still being treated. As the treatment time was delayed, the survival rate might be further reduced.

Table 4. Correlation analysis of Immunophenotype and prognosis

prognosis	Immunophenotype		P value
	B-ALL	T-ALL	
death	4	2	0.038
survival	41	11	

Table 5. Correlation analysis of chromosome karyotype and prognosis

prognosis	chromosome karyotype		χ^2 value	P value
	normal	abnormal		
death	2	4	4.114	0.043
survival	28	14		

Table 6. Correlation analysis of chromosome fusion genes and prognosis

prognosis	fusion genes		χ^2 value	P value
	positive	negative		
death	3	3	1.016	0.313
survival	9	33		

Gender and age of onset are the prognostic factors affecting children with ALL. Boys have a higher incidence than girls, and boys have a worse prognosis than girls. In formulating the chemotherapy plan, less than 1 year old or more than 10 years old is a poor prognostic factor[5]. Our statistical results show that, in terms of incidence, 64.6 % of boys and 35.4% of girls were in line with relevant literature[6]. Although this study has no statistical significance on the correlation analysis of gender, age and prognosis (P> 0.05), but considering the small sample size, the statistical analysis of large samples still needs to be further clarified.

Acute lymphoblastic leukemia is divided into B-ALL and T-ALL according to the differentiation of cell surface differentiation antigens. B-ALL is the most common type of childhood ALL, and its prognosis is better than T-ALL. Immunotyping for T subtype is one of the intermediate risk indicators. The prognosis of T subtype is worse than that of B subtype[7]. A total of

43 cases of B-ALL (93.75%) and 3 cases of T-ALL (6.25%) were collected in this article, of which 6 people died, of which 4 cases of B-ALL died, 3 cases were high-risk, 2 cases died of remission after relapse. One case died of infection, and the other one was low-risk and died of infection. Two cases of T-ALL died from infection. The statistical results show that immunophenotyping has statistical significance for the prognosis, the prognosis of B-ALL is better than T-ALL.

In abnormal chromosome numbers, children with hyperdiploid are sensitive to chemotherapy drugs[8]. The incidence of hyperdiploid ALL is about 27%, with a high cure rate, but a high recurrence rate[9]. In this group, 6 cases of hyperdiploid were detected, and the detection rate was 12.5%, which was significantly lower than that reported in the literature. Except for 1 case died of infection, the remaining 5 cases of hyperdiploid children are still free of disease. A total of 18 children with chromosomal abnormalities were collected in this study, of which 4 died. The analysis found that chromosomal abnormalities were associated with poor prognosis.

It is reported in the literature that about 85% of children with leukemia can detect clonal chromosomal abnormalities and lead to fusion genes[10]. The existence of specific translocations of fusion genes has proved to play an important role in the malignant transformation of leukemia. The detection of fusion genes can help to stratify the risk of childhood leukemia, determine the prognosis, and help to choose the appropriate chemotherapy regimen. The positive rate of ALL children in this group reached 25%, and a total of 5 leukemia fusion genes were detected, including TEL/AML1, MLL/AF4, E2A/PBX1, MLL/AF9 and FLT3-ITD.

t (12; 21) (p13; q22) chromosome translocation, forming the fusion gene TEL/AML1 is the most common in children with ALL, about 25% of children with acute lymphoblastic leukemia, the fusion gene is positive, which is considered to be low in children with ALL Critical indicators, more suggest that the prognosis is better[11]. A total of 12 cases of gene mutations were collected in this study, of which 5 cases were positive for the TEL/AML1 fusion gene, and all are now disease-free. t (1; 19) (q23; p13) chromosome translocation-forming fusion gene E2A/PBX1 accounts for 3% to 5% of children ALL, mostly B-ALL, and rare in T-ALL[12]. The positive E2A/PBX1 fusion gene has a more dangerous clinical symptom, suggesting that the child has a poor prognosis. If the gene is still positive after treatment, the later recurrence rate is higher[13]. In this group of 13 ALL children with E2A/PBX, the positive rate was 6.25%, slightly higher than that reported in the literature, and it is not ruled out that it is related to the small number of cases in this group. MLL gene rearrangement accounts for 2% to 6% of childhood ALL, most of which occurs in infancy, and is rare in other age groups[14]. There are many partner genes related to MLL, and the two common types are AF9 and AF4. In this study, 3 children with ALL were rearranged to MLL, with a positive rate of 6.25%, suggesting that leukemia was highly malignant and often has a poor prognosis. The prognosis of the fusion gene abnormalities in this study was not different from the normal. Considering that this was due to the small sample size, the statistical analysis of large samples still needs to be further clarified.

5. Conclusion

The age and sex of children, as well as leukemia immunotyping, karyotype, and fusion gene detection are important for the treatment and prognosis of children with ALL. Reasonable analysis of leukemia immunotyping, chromosomal nuclei Type and fusion gene test results can help improve the diagnosis and treatment of childhood leukemia, and adjust and guide treatment programs to improve the survival rate of children.

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