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Allogeneic blood transfusion in 163 children with acute lymphocytic leukemia (a STROBE-compliant article)

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Abstract

Little research has been done about the effects of allogeneic blood transfusion (ABT) on the recurrence and prognosis in the cases with childhood acute lymphocytic leukemia (cALL). In order to provide a basis for clinical safe blood transfusion, the data of 163 cases with cALL were retrospectively analyzed to explore the issue.

The data of 163 cases with cALL between 2006 and 2011 were retrospectively analyzed. According to the frequency of blood transfusion, the 163 cases were divided into 4 groups including non-transfusion group, 1 to 10-time transfusion group, 11 to 25-time transfusion group, and >25-time transfusion group. Survival rates were compared with Log-Rank test. Cox regression analysis was used in the effects of risk factors on recurrence and death.

ABT was performed in 152 cases with cALL (93.25%). In low-risk and intermediate-and-high risk cALL, the survival rate significantly decreased in all transfusion groups compared with that in non-transfusion group (all $P < .01$). Cox regression analysis showed that >25-time transfusion was an independent prognosis index of recurrence (odds ratio [OR] = 3.015, 95% confidence interval [CI]: 1.368–6.646) and death (OR = 3.979, 95% CI: 1.930–8.207) in cALL.

Frequency of ABT appears to affect the recurrence and death in cALL. We should be careful with blood transfusion and avoid unnecessary blood transfusion as far as possible in the cases with cALL.

Abbreviations: ABT = allogeneic blood transfusion, ALL = acute lymphocytic leukemia, cALL = childhood acute lymphocytic leukemia, HR-ALL = high risk acute lymphocytic leukemia, IR-ALL = intermediate risk acute lymphocytic leukemia, LR-ALL = low risk acute lymphocytic leukemia, PRBCs = packed red blood cells, SDPs = single donor platelets, sFasL = soluble Fas ligand, TRIM = transfusion-related immunomodulation.

Keywords: allogeneic blood transfusion, childhood acute lymphocytic leukemia, prognosis, recurrence

1. Introduction

Long-term chronic consumption and bone marrow function suppression caused by chemotherapy inevitably lead to hematocytopenia in the cases with childhood acute lymphocytic leukemia (cALL). Allogenic blood transfusion (ABT) is a kind of common supporting therapy and >90% of cases with cALL require ABT. Blood transfusion can bring some risks including blood-borne disease, immunosuppressive effects, blood transfusion-induced pulmonary injury, non-hemolytic fever, and anaphylaxis.[1–3] With the development of the screening technology for blood-borne microbes, the incidence of blood-borne disease has been markedly decreased. Therefore, a great deal of attention has been paid to transfusion-related immunomodulation (TRIM). There are some reports about beneficial results produced by TRIM. For example, preoperative ABT can improve the survival rate in the patients undergoing renal transplantation,[4] ABT can decrease the recurrence of Crohn disease,[5] and can reduce the risk of recurrent and spontaneous abortion.[6] However, TRIM also can produce adverse clinical effects, namely that it can inhibit recipients' immune function and decrease recipients' immune surveillance function. It is reported that ABT is markedly associated with tumor recurrence and metastasis, mortality, and postoperative infection; and the prognosis is poorer and tumor recurrence rate is higher in the patients with ABT than in the patients without ABT.[7–10] However, there also are some reports that ABT is not related to recurrence and prognosis in the patients with tumor.[11,12]

The features of TRIM have not been clear in cALL and little research has been done about the effects of ABT on the recurrence and prognosis in the cases with cALL. The purpose of our current study is to explore the effects of ABT on the recurrence and prognosis of cALL, providing a basis for clinical safe blood transfusion.

2. Subjects and methods

All study methods were approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

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2.1. Subjects

The data of 186 cases who were first diagnosed with cALL according to "Diagnosis and treatment for childhood acute lymphoblastic leukemia"[13] made by the hematology group, pediatrics branch, Chinese Medical Association between January 2006 and March 2011 were reviewed. These cases were followed up between January 2006 and October 2011 with a follow-up period of 1 to 70 months. Twenty three cases were lost to follow up. The remaining 163 cases were enrolled in this study.

2.2. Study design

Bone marrow cell morphology, cytogenetics, and immunophenotyping were performed in the 163 cases. Clinical risk rating was divided into low-risk, intermediate-risk, and high-risk cALL according to clinical risk factors.[14] Treatment protocols were made according to clinical risk rating.[13] During chemotherapy, component blood transfusion was performed, in detail, concentrated red blood cell transfusion was performed in the cases with hemoglobin <60 g/L or packed red cell volume <0.20, apheresis platelet transfusion was performed in the cases with platelets $<10\times10^9$/L or bleeding tendency, and fresh frozen plasma or cryoprecipitation transfusion was performed in the cases with blood clotting abnormality.

2.3. Risk stratification criteria

The risk stratification includes low, intermediate, and high risks.

High risk acute lymphocytic leukemia (HR-ALL) includes one or more of the following items: age <1 year; peripheral white blood cell $\geq100\times10^9$/L; karyotype of *t* (9; 22), BCR-ABL fusion gene, *t* (4; 11), and (or) MLL-AF4 fusion gene; poor prednisone responder; and (or) initial treatment-induced remission failure.

Intermediate risk acute lymphocytic leukemia (IR-ALL) includes one or more the following items: age ≥10 years; peripheral white blood cell $\geq50\times10^9$/L; having central nervous system leukemia and (or) testis leukemia; T cell leukemia; hypodiploid with chromosome number <45, other abnormal karyotypes besides *t* (12; 21) and *t* (9; 22), or other MLL gene rearrangements besides *t* (4; 11).

Low risk acute lymphocytic leukemia (LR-ALL) has no any item in HR-ALL and IR-ALL.

2.4. The source of blood products

The blood products were provided by the Blood Center of Red Cross in Henan Province. Various blood components were obtained by routine procedures from donors and were treated by leukapheresis without γ-laser radiation. Each therapeutic dose of apheresis platelet was 200 mL containing $>2.5\times10^{11}$ platelets. The red blood cells prepared with 200 mL of whole blood were regarded as one unit.

2.5. Transfusion protocol

For the children with hemoglobin <60 g/L or hematocrit <0.20, concentrated red blood cells were infused. RBC dose (U)= [expected Hb value (g/L)−Hb value (g/L) before infusion] × body weight (kg) × 0.08/20. For the children with bleeding tendency or $<20\times10^9$ of platelets, platelets of about 2.5 to 3.64×10^{11} were infused. For the children with abnormal hemagglutination function, fresh frozen plasma of 10 to 15 mL/kg or cryoprecipitation of 1 to 1.5 U/10 kg were given.

2.6. Statistical data

Based on the medical records and follow-up data, sex, age, immunophenotyping, peripheral blood WBC count in newly diagnosed cALL ($>50\times10^9$/L or $<50\times10^9$/L), recurrence, prognosis, and the frequency of blood product transfusion (blood products included packed red blood cells or platelets or fresh frozen plasma, and the same case might receive multiple transfusions). According to the frequency of blood transfusion, the 163 cases were first divided into 4 groups including non-transfusion group, 1 to 10-time transfusion group, 11 to 25-time transfusion group, and >25-time transfusion group, and then the recurrence and death rates were compared among the 4 groups. It is known that the different clinical risks are associated with survival rate of the cases with cALL. In order to exclude the effect of different clinical risk factors on survival rates of the cases with cALL, the cases with cALL were first divided into low-risk group and intermediate-and-high risk group, and then were again divided into 4 groups including non-transfusion group, 1 to 10-time transfusion group, 11 to 25-time transfusion group, and >25-time transfusion group in the 2 groups followed by Kaplan–Meier survival analysis, exploring the correlation between the frequency of blood transfusion and survival rate. Cox regression analysis was used in the effects of risk factors on recurrence and death.

2.7. Statistical analysis

Statistical analysis was performed with SPSS19.0 software (IBM, Armonk, New York). Kaplan–Meier method was used in survival analysis. Survival rates were compared with Log-Rank test. Cox proportional hazards model was used in the analysis of single risk factor and multiple risk factors. Spearman was used in non-parametric bivariate correlation analysis. Statistical significance was established at $P<.05$. The overall survival time was from the date of diagnosis until the date of the last follow-up date or the date of death.

3. Results

3.1. Demographic and clinical characteristics of patients

Of the 163 cases, 102 were men and 61 women (the ratio of men to women: 1.67:1), with a mean age of 5 years (range, 0.6–14). Of the 163 cases, 136 cases had B-cell acute lymphoblastic leukemia (B-ALL) and 27 had T-cell acute lymphoblastic leukemia (T-ALL), 69 cases belonged to low-risk cALL, and 94 cases belonged to intermediate-and-high risk cALL. The average follow-up period was 25.47 months (range, 1–70 mo). Until the end of follow-up, recurrence occurred in 42 cases (25.77%, 42/163) including 29 cases with bone marrow relapse (17.79%, 29/163), 9 cases with central nervous system relapse (5.52%, 9/163), 3 cases with testicular relapse (1.84%, 3/163), and 1 case with mixed relapse (0.61%, 1/163). Of the 42 cases, 19 cases died, 7 cases survived after bone marrow stem cell transplantation, and 16 cases were survival after repeated chemotherapy. The overall death rate was 23.31% (38/163). The clinical features of all cases are shown in Table 1.

3.2. Recurrence and death rates in the 4 groups

With the elevation of the frequency of blood transfusion, the recurrence and death rates increased. There were no statistical differences in the recurrence and death rates between

Table 1

Clinical features and transfusion status in 163 cases with childhood acute lymphocytic leukemia.

Clinical features	n	(%)	Transfusion		Non-transfusion		X^2	P
			n	%	n	%		
Total cases	163		152	93.25%	11	6.75%		
Sex								
Male	102	62.58%	96	94.12%	6	5.88%	0.325	.569
Female	61	37.42%	56	91.80%	5	8.20%		
Age								
1–10 y	136	83.44%	125	91.91%	11	8.09%	2.342	.126
<1 y or >10 y	27	16.56%	27	100.00%	0	0.00%		
Immunophenotype								
B-cell	147	90.18%	136	92.52%	11	8.09%	1.284	.257
T-cell	16	9.82%	16	100.00%	0	0.00%		
WBC count								
$<50\times10^9$	86	52.76%	77	89.53%	9	10.47%	3.996	.046
$\geq50\times10^9$	77	47.24%	75	97.40%	2	2.60%		
Clinical risk rate								
LR	69	42.33%	62	89.86%	7	10.14%	4.111	.128
MR	55	33.74%	51	92.73%	4	7.27%		
HR	39	23.93%	39	100.00%	0	0.00%		

LR = lymphocytic leukemia, HR = high risk, WBC = white blood cell.

non-transfusion group and 1 to 10-time transfusion as well as 11 to 25-time transfusion groups (all $P > .05$), but the recurrence and death rates were significantly higher in the >25-time transfusion group (64.29% and 60.71%) than in other 3 groups (all $P < .01$) (Table 2).

3.3. Effects of blood transfusion on the survival rate

In this study, there were 69 cases with low risk cALL and 94 cases with intermediate-and-high risk cALL. In the cases with low risk cALL, the 3-year overall survival rates were 100% in the non-transfusion group, 95% in the 1 to 10-time transfusion group, 89% in the 11 to 25-time transfusion group, and 54% in the >25-time transfusion group. The 3-year overall survival rate was higher in the non-transfusion group (100%) than in others 3 groups (95%, 89%, and 54%), especially in the >25-time transfusion group ($P = .004$, Log-Rank = 13.198 obtained by Kaplan–Meier method). With the increase in the frequency of blood transfusion, the overall survival rates were decreased in the cases with low risk cALL (Fig. 1). In the cases with intermediate-and-high risk cALL, the tendency of 3-year overall survival rate was similar to that in the cases with low-risk cALL ($P = .005$, Log-Rank = 13.017 obtained by Kaplan–Meier method) (Fig. 2). Spearman method indicated that the frequency of blood transfusion was strongly associated with survival variate ($r_s = 0.423$, $P < .01$).

Table 2

Comparisons of recurrence and death rates in the 4 groups.

Groups	n	Recurrence	Death
Non-transfusion	11	1 (9.09%)	0 (0.00%)
1 to 10-time transfusion	55	7 (12.73%)	6 (10.91%)
11 to 25-time transfusion	69	15 (21.74%)	16 (23.19%)
More than 25-time transfusion	28	18 (64.29%)	17 (60.71%)
X^2		29.221	29.419
P		.000	.000

3.4. Cox regression analysis of recurrence and death-related factors

Univariate Cox regression analysis indicated that the relative risk values of age, sex, immunophenotype, clinical risk rating, peripheral blood WBC count, and the frequency of blood transfusion all were >1, demonstrating that these factors all are related to recurrence and death. However, univariate and multivariate Cox regression analysis indicated that >25-time transfusion (odds ratio [OR] = 3.015, $P = .006$) and immunophenotype (OR = 3.632, $P = .002$) were the independent prognosis indexes of recurrence in the cases with cALL. Multivariate Cox regression analyses of death-related factors showed that >25-time transfusion (OR = 3.015, $P = .006$) and clinical risk rating (OR = 3.015, $P = .006$) were the independent prognosis indexes of death in the cases with cALL (Table 3).

4. Discussion

The blood as a substance of immunogenicity and reactionogenicity necessarily causes a series of immune regulation reactions.[14] Allogeneic blood transfusions may cause alloimmunization, tolerance, or immunosuppression. The immunosuppressive effects caused by ABT in recipients are termed as TRIM. TRIM can produce adverse clinical effects. For example, immune function is inhibited and immune surveillance function is decreased in recipients,[15,16] so theoretically TRIM could contribute to cancer progression.

However, there were different reports. Freiberg et al[17] believed that the high frequency of transfusions was an epiphenomenon that reflected other factors such as disease severity and reduction of chemotherapeutic effect, and TRIM effect unlikely happened in these patients. Recently, Alkayed et al[18] retrospectively studied 136 children with ALL that possibly had TRIM during the induction phase, 120 patients (89%) were transfused with packed red blood cells (PRBCs), and 79 (58%) with single donor platelets (SDPs), and univariate analysis indicated that PRBC, SDP, and fresh frozen plasma transfusions did not have any significant association with relapse

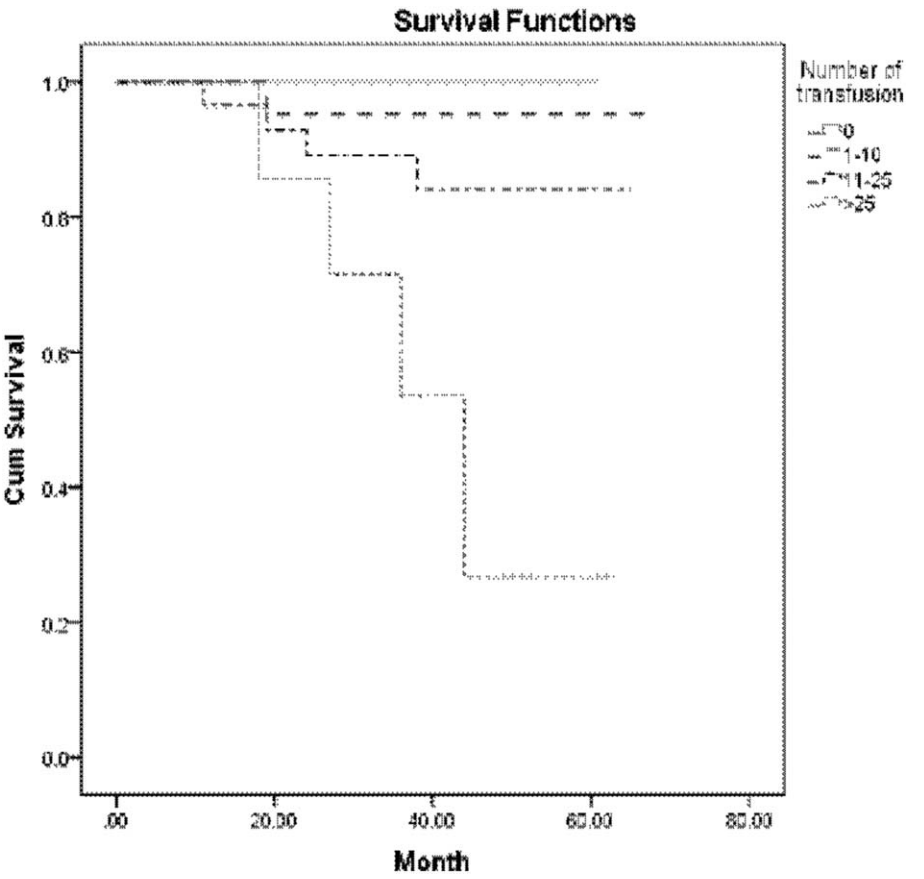

Figure 1. The overall survival rates of non-transfusion group, 1 to 10-time transfusion group, 11 to 25-time transfusion group, and >25-time transfusion group in the cases with low-risk cALL. The overall survival rate is the lowest in >25-time group. Compared with non-trasfusion group, the overall rates are significantly decreased in transfusion groups (Log-Rank = 13.198, $P = .004$).

or death. However, Jaime-Pérez et al[15] retrospectively studied 108 children with ALL diagnosed between 2000 and 2009 to explore the relationship between TRIM and prognosis in cALL and believed that the frequency of blood transfusion was predictive of death and relapse, and TRIM may be an independent prognostic factor in cALL.

It is known that the clinical risk is the higher, the prognosis is the worse in the cases with cALL. In order to exclude the effect of different clinical risk factors on survival rates of the cases with cALL, we performed Kaplan–Meier survival analysis after stratification of clinical risks. Our results indicated that in both low-risk and intermediate-and-high risk cALL, with the increase in the frequency of blood transfusion, the survival rate was decreased ($P < .01$); and survival rate was strongly associated with the frequency of blood transfusion ($P < .01$); suggesting that frequent blood transfusion may be an independent predictor of poorer prognosis for cALL. Our results are consistent with that from Jaime-Pèrez et al,[15] demonstrating that ABT most possibly affects the survival rate of the cases with cALL.

There are many factors affecting recurrence and prognosis of cALL. In order to verify the roles of these factors, univariate and multivariable Cox proportional hazards model was used in the analysis of these factors. Our results indicated that >25-time transfusion and clinical risk rating were the independent prognosis indexes of death in the cases with cALL, and the relative risk values of frequency of blood transfusion (OR = 3.973, $P < .01$) was the highest, suggesting that the frequency of blood transfusion is the main factor affecting prognosis. The results about recurrence-related factors indicated that >25-time blood transfusion and immunophenotype were the independent prognosis indexes of recurrence in the cases with cALL (OR = 4.079, $P < .01$), suggesting that the high frequency of transfusion is the main factor affecting recurrence. In short, the frequency of blood transfusion may be an independent prognosis index of recurrence and prognosis in the cases with cALL.

Our conclusion is similar to that of Jaime-Pérez et al,[15] but different from those of Freiberg et al[17] and Alkayed et al.[18] One of the reasons for the discrepancy between these studies might be due to different blood preparation methods. The blood products in the studies by Freiberg et al[17] and by Alkayed et al[18] were treated by leukapheresis and γ-laser radiation, whereas only leukocyte-reduced products were used in the study by Jaime-Pérez et al.[15] The blood product used in this study was also only treated by leukapheresis. Irradiation might prevent mononuclear cell proliferation which is necessary for TRIM. TRIM caused by ABT might affect the prognosis of cALL.

Most studies suggest that the reduction of survival rate and the elevation of recurrence caused by ABT are related to transfusion-associated immunosuppressive effects.[7–9] However, the transfusion-associated immune suppression fails to be clearly explained now. Claas et al[16] believed that ABT can affect recipients' specific and nonspecific immune. Blood products including concentrated red blood cells, blood platelets, and blood plasma contain a few white blood cells and these white blood cells

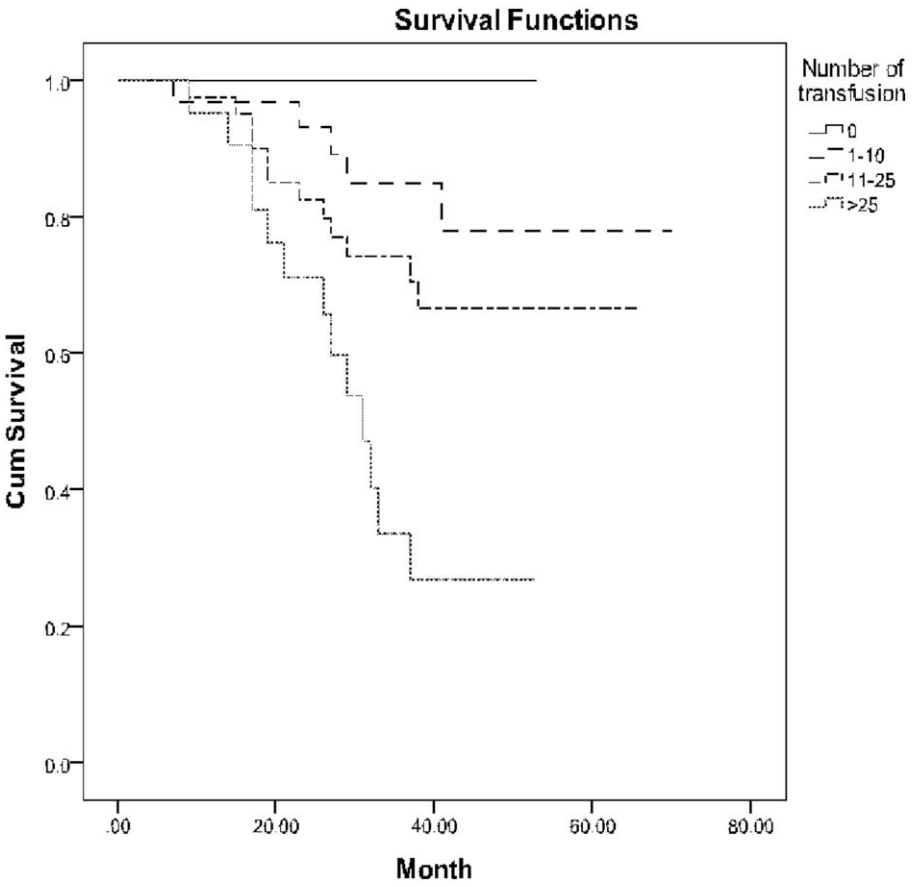

Figure 2. The overall survival rates of non-transfusion group, 1 to 10-time transfusion group, 11 to 25-time transfusion group, and >25-time transfusion group in the cases with intermediate-and-high risk cALL. The overall survival rate is the lowest in >25-time group. Compared with non-trasfusion group, the overall rates are significantly decreased in transfusion groups (Log-Rank = 13.017, $P = .005$).

can release bioactive molecules such as histamine, inflammatory factors, TNF-α, sHLA, soluble Fas ligand (sFasL) during storage.[19–21] When recipients receive blood transfusion, these bioactive molecules induce the secretion of transforming growth factor (TGF)-β, interleukin (IL)-4, and IL-10, and inhibit the secretion of IL-2 and interferon (IFN)-γ,[22,23] leading to recipients' immune suppression. Suspended allogeneic red cells can also release arginase which inhibits recipients' lymphocyte

Table 3

Univariate and multivariate Cox regression analyses of these recurrence and death-related factors in the cases with childhood acute lymphocytic leukemia.

		Death				Recurrence			
Risk factors	**n**	**Unadjusted OR (CI 95%)**	***P***	**Adjusted OR (CI 95%)**	***P***	**Unadjusted OR (CI 95%)**	***P***	**Adjusted OR (CI 95%)**	***P***
Sex									
Male	102	0.735 (0.375–1.513)	.426	0.890 (0.437–1.813)	.749	0.915 (0.478–1.751)	.787	1.192 (0.610–2.332)	.607
Female	61								
Age, y									
1–10		2.191 (1.089–4.406)	.028	1.274 (0.591–2.745)	.537	1.701 (0.829–3.494)	.148	0.847 (0.372–1.928)	.692
<1 or >10									
Immunophenotyping									
B-cells	147	3.309 (1.731–6.327)	.000	1.717 (0.776–3.795)	.182	5.907 (3.021–11.553)	.000	3.632 (1.602–8.236)	.002
T-cells	16								
WBC									
$<50 \times 10^9$	86	2.014 (1.062–3.819)	.032	0.543 (0.213–1.382)	.200	2.061 (1.105–3.845)	.023	.602 (0.244–1.489)	.272
$\geq 50 \times 10^9$	77								
Risk rating									
Low	69	2.750 (1.304–5.800)	.008	2.632 (0.923–7.506)	.070	3.059 (1.454–6.435)	.003	2.522 (0.919–6.920)	.072
Middle or High	94								
Frequency of transfusion									
≤25	135	4.682 (2.479–8.842)	.000	3.979 (1.930–8.207)	.000	4.487 (2.266–8.885)	.000	3.015 (1.368–6.646)	.006
>25	28								

function and decrease recipients' immune function.[24] In addition, platelet suspension liquid contain platelet-derived bioactive molecules such as plasminogen activator inhibitor-1, tissue inhibitor of metalloproteinase-1, vascular endothelial growth factor, and these molecules can inhibit the function of neutrophilic granulocytes and play an important role in the transfusion-related immunosuppressive effect.[25] In short, many bioactive molecules in blood products are involved in recipients' immunosuppressive effect, and what factors play a leading role has been controversial.

There were some limitations in our study. Firstly, because of the small sample size and retrospective design, a relationship between cause and effect could not be proven. Secondly, the storage time of blood products transfused was not considered. Therefore, it is necessary for our results to be further validated by prospective studies.

In summary, our results suggest that blood transfusion appears to affect recurrence and prognosis in cALL, but this mechanism has not been clear and may be associated with above factors-mediated transfusion-related immunosuppressive effect. In clinical practice, the adverse effects of ABT are often ignored by clinicians or contributed to cALL complications. Therefore, we suppose that clinicians should pay attention to the adverse effects of ABT, try to avoid unnecessary ABT, use recombinant erythropoietin or granulocyte colony-stimulating factor as far as possible in the treatment of cALL.

Author contributions

Data curation: Ge Zhou.
Investigation: Jiao Chen.
Methodology: Shu-ting Mao.
Writing – original draft: Dao Wang.
Writing – review & editing: Yu-feng Liu.

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