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Clinical analysis of immune reconstitution after chemotherapy in children with acute lymphoblastic leukemia

Yuting Xu[1], Ai Zhang[1], Aiguo Liu[1] and Qun Hu[1*]

Abstract

Objectives The aim of this retrospective study was to investigate the influence of chemotherapy on the immune status of individual patients diagnosed with acute lymphoblastic leukemia (ALL) and to elucidate the clinical characteristics of immune reconstitution in ALL patients following chemotherapy.

Methods Clinical data of children with ALL were gathered, including information on the number of lymphocyte subsets prior to chemotherapy, at the end of therapy, six months, and one year after the end of the treatment.

Results A total of 146 children with ALL were included, and T cells, B cells, and NK cells all decreased to various degrees prior to treatment. The abnormal CD3 + T cell numbers group experienced a considerably higher mortality (21.9% vs. 6.1%) and recurrence rate (31.3% vs. 11.4%) compared to the normal group ($P < 0.05$). T cells, B cells, and NK cells were all significantly compromised at the end of therapy compared to the beginning of chemotherapy, with B cells being more severely compromised ($P < 0.001$). At the end of treatment, levels of B cells, CD4 + T cells, CD4/CD8, IgG and IgM in low risk (LR) group were significantly higher than those in intermediate risk (IR) group ($P < 0.01$), and levels of NK cells in LR group were evidently lower than those in IR group ($P < 0.001$). Six months after the end of therapy, all the above indicators recovered ($P < 0.001$) except CD4/CD8 ratio ($P = 0.451$).

Conclusions The immune systems of the ALL patients were severely compromised upon therapy withdrawal, particularly the B cells. At six months after the therapy ended, the B cells were basically restored to normal level, while the T-cell compartment was not. The impaired numbers of CD3 + T cell may contribute to a weakened anti-tumor response, potentially leading to a poorer prognosis.

Keywords Acute lymphoblastic leukemia, Chemotherapy, B cells, T cells, NK cells, Immune reconstitution

*Correspondence:
Qun Hu
qunhu2013@163.com
[1]Department of Pediatric Hematology and Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Introduction

Acute lymphoblastic leukemia (ALL) is the predominant malignancy in childhood, comprising approximately 28% of childhood malignancies [1]. ALL encompasses B cell lines (85%), T cell lines (10-15%) and mature B cell lines (<5%). The global incidence of this disease exhibits slight variation due to diagnostic and reporting methodologies, with a peak occurrence in children aged 2 to 5 years, and a higher prevalence in males [2–5]. Currently, the primary treatment modality for pediatric ALL is chemotherapy, typically administered within 2 to 3 years. Chemotherapy protocol primarily consists of an induction phase (more than a month), followed by consolidation (two months) and re-induction (more than four months) therapy, then maintenance phase (nearly 2 years; 6-mercaptopurine and methotrexate are the backbone of maintenance phase).

The initial maturation of B lymphocytes involves the orchestrated differentiation of B cells and the subsequent expression of surface immunoglobulin (Ig). Following this process, immature B cells exit the bone marrow and migrate to secondary lymphoid tissues [6–8]. CD19 is a kind of cluster differentiation antigen related to proliferation, differentiation, activation, and antibody production of B cells. Various surface markers are expressed on B cells at distinct developmental stages, with CD19 being a key component of a multi-molecular surface complex that plays a crucial role in antigen response and signal transduction in T helper cells [9, 10]. It is noteworthy that a significant majority of leukemia cells exhibit high expression levels of CD19 [11]. CD20, a transmembrane protein found in lipid rafts, is phosphorylated four times and functions as a calcium channel to modulate B cell activation and cell cycle progression [12, 13]. CD19 and CD20 are commonly used markers for counting B cells. T cells primarily mature in the thymus and over 95% of circulating T cells express T cell surface receptors with α and β chains [14]. CD3 molecules play a crucial role in T cell signal transduction upon binding to T cell surface receptors, with CD3 serving as the primary marker for quantifying total T cells. CD4+T cells and CD8+T cells are the two most common subsets of T lymphocytes, as well as some other less common subsets. CD4 belongs to the Ig superfamily and interacts with class II molecules of the major histocompatibility complex, while CD8 interacts with class I molecules of the major histocompatibility complex. Natural killer (NK) cells are innate immune cells with distinctive functions, lacking antigen-specific receptors but expressing a range of activation and inhibition receptors [15]. Among these receptors, activation receptors play a crucial role in the cytotoxic activity of NK cells [16, 17]. NK cells affect the host's innate and adaptive immune responses by secreting cytokines and chemokines, and then kill infected or cancerous cells through a variety of mechanisms.

The ongoing advancements in contemporary risk-oriented therapy and the introduction of novel treatments have led to a notable increase in the 5-year survival rate of children diagnosed with ALL, rising from 50–85-90% [2, 18, 19]. This study aims to examine the immune status of pediatric ALL patients prior to commencing chemotherapy and the subsequent recovery of immune cells at various intervals post-treatment. The objective is to furnish empirical evidence supporting immune reconstitution in children with ALL after chemotherapy and to develop pertinent rehabilitation strategies.

Materials and methods

This research involved a cohort of 146 children diagnosed with ALL who underwent immune function testing at Tongji Hospital, affiliated to Tongji Medical College, Huazhong University of Science and Technology, between January 2015 and May 2019, with follow-up conducted until November 2021. All children were diagnosed based on the guidelines outlined by the National Comprehensive Cancer Network Pediatric Acute Lymphoblastic Leukemia [20]. Patients were stratified into three risk groups (low risk, intermediate risk, and high risk) based on clinical, biological, and therapeutic responses. Please refer to supplementary Table 1 for specific hierarchical details. The enrolled children began to receive treatment with Chinese Children's Cancer Group ALL-2015 (CCCG-ALL-2015) protocol after diagnosis, which mainly included the following parts: window phase, PVDL induction, consolidation therapy, interim maintenance, reinduction and maintenance therapy (see supplementary Table 2 and supplementary file). The trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IPR-14005706) on June 4th, 2014. Approval for this study was obtained from the Ethics Committee of Tongji Hospital, affiliated with Tongji Medical College, Huazhong University of Science and Technology, and informed consent was obtained from the guardians or the individuals themselves (reference no. 2020-S207).

The study assessed NK cells and the T-cell compartment, including CD3+T cells, CD4+T cells, CD8+T cells, and CD4/CD8 ratio, as well as the B cells and immunoglobulin levels, in children diagnosed with ALL at four time points: before treatment (E1), at the end of treatment (E2), 6 months post-treatment (E3), and 12 months post-treatment (E4).

Flow cytometry was used to analyze the absolute values and percentages of peripheral blood lymphocyte subsets, including T cells, B cells, and NK cells. The BD FACSCalibur flow analyzer was utilized in conjunction with corresponding fluorescent monoclonal antibodies (CD3FITC, CD16CD56PE, CD4PE-Cy7, CD8APC-Cy7, CD19APC)

Table 1 Demographic and clinical characteristics of children with ALL before treatment

Characteristic	Number
Gender, n(%)	
Male	91(62.3)
Female	55(37.7)
Age/year, M(Min-Max)	4.7(1.3–14.3)
Height/cm, M(IQR)	108.0(96.0-120.2)
Weight/kg, M(IQR)	18.0(15.0–23.0)
BMI/kg/m^2, M(IQR)	15.8(14.9–16.9)
Risk, n(%)	
LR	73(50)
IR/HR	73(50)
Immunotyping, n(%)	
B-ALL	130(89)
T-ALL	16(11)

and hemolysin from BD for the analysis. Fasting peripheral venous blood samples of 2 ~ 3mL were collected with heparin anticoagulation and stored at room temperature for analysis within 24 h. A total of 50mL of anticoagulant and 10mL of fluorescence-labeled antibodies were added to a specialized test tube, mixed thoroughly, and allowed to incubate at room temperature for 15 min. Subsequently, 450mL of hemolysin was added, followed by a 5-minute incubation away from light, and the computer system was used for analysis. The level of immunoglobulin was assessed using Beckman immune scattering turbidimetry, with serum samples of 3 ~ 5mL collected for analysis.

The data were analyzed by SPSS 26.0 software. Data following a normal distribution were presented as mean ± standard deviation, while non-normal distribution data were presented as median (M) and interquartile range (IQR), and categorical data were expressed as percentages. The Mann-Whitney U test was used to analyze quantitative data for two independent samples, the Wilcoxon signed rank test for paired samples, and the chi-squared test for categorical data. $P<0.05$ was considered statistically significant.

Results

Analysis of immune cells before chemotherapy

A total of 146 children diagnosed with ALL were included in the study, with the clinical features detailed in Table 1.

Prior to treatment, there was no statistically significant variance in immune cells observed among children based on gender (T-cell compartment, B cells, NK cells, and all immunoglobulin subclasses). However, children classified as LR exhibited significantly lower levels of CD8 + T cells ($P=0.020$) and NK cells ($P<0.001$) compared to those classified as IR/HR. Additionally, children diagnosed with B-ALL demonstrated evidently higher levels of CD3 + T cells ($P=0.020$), CD4 + T cells ($P=0.004$), CD4/CD8 ratio ($P=0.034$), and B cells compared to those diagnosed with T-ALL ($P=0.019$, Table 2).

Out of the 146 cases ALL examined, 14 cases died and the mortality was 9.5%, 3 cases died from treatment-related complications (severe infection leading to septic shock) and 11 cases died from disease progression (9 cases died after relapse and 2 cases died during

Table 2 Analysis of immune cells of children with different risk and immunophenotype before chemotherapy

	Risk			Immunophenotype		
	LR (*n* = 73)	**I/HR (*n* = 73)**	***P***	**B-ALL (*n* = 130)**	**T-ALL (*n* = 16)**	***P***
CD3 + T cells	1477 (1040–2550)	2137 (998–3223)	0.065	1907 (1131–2765)	1025 (429–2369)	**0.020**
NK cells	166 (78–265)	283 (113–660)	**0.001**	197 (86–394)	280 (89-1129)	0.312
CD4 + T cells	811 (545–1221)	920 (530–1696)	0.308	890 (581–1534)	453 (252–970)	**0.004**
CD8 + T cells	621 (410–844)	820 (418–1543)	**0.020**	733 (431–1107)	455 (147–973)	0.069
CD4/CD8	1.36 (1.06–1.68)	1.14 (0.84–1.71)	0.054	1.27 (1.02–1.70)	0.96 (0.79–1.32)	**0.034**
B cells	422 (203–716)	631 (204–1108)	0.095	525 (236–1013)	161 (65–695)	**0.019**
IgA	0.78 (0.47–1.07)	0.70 (0.54–1.21)	0.731	0.73 (0.51–1.08)	0.79 (0.52–1.22)	0.584
IgG	8.70 (7.55–10.65)	9.00 (7.30-10.45)	0.891	9.10 (7.37–10.60)	8.35 (7.35–9.72)	0.259
IgM	0.91 (0.71–1.12)	0.84 (0.60–1.19)	0.661	0.91 (0.70–1.13)	0.73 (0.50–1.57)	0.267

The bold fonts describes the difference in the number of immune cells in patients with different risk levels (low risk, intermediate risk, high risk) and different immunophenotypes before chemotherapy

treatment). A total of 23 patients experienced relapses (15.7%), in which 14 cases exhibited bone marrow recurrence, 6 cases had central nervous system recurrence, and 3 cases had mixed recurrence (involving both bone marrow and central nervous system). Statistical analysis revealed that the mortality rate ($P=0.02$) and recurrence rate ($P=0.006$) were significantly higher in children with abnormal CD3+T cell numbers (outside the normal range) prior to chemotherapy compared to those in the normal group (Fig. 1).

Analysis of immune cells at the end of chemotherapy

Fifteen patients withdrew from the study for various reasons (such as voluntary abandonment or transfer to another hospital), while the remaining participants successfully completed the treatment regimen. The median duration of treatment was 2.5 years. Following chemotherapy, bone marrow assessment indicated complete remission, and blood routine parameters returned to baseline levels. The study has shown that the immune cells in children with ALL decreased distinctly after chemotherapy, particularly the levels of CD4/CD8 (69/131, 52.7%), NK cells (82/131, 62.6%), B cells (112/131, 85.5%), and IgM (98/131, 74.8%).

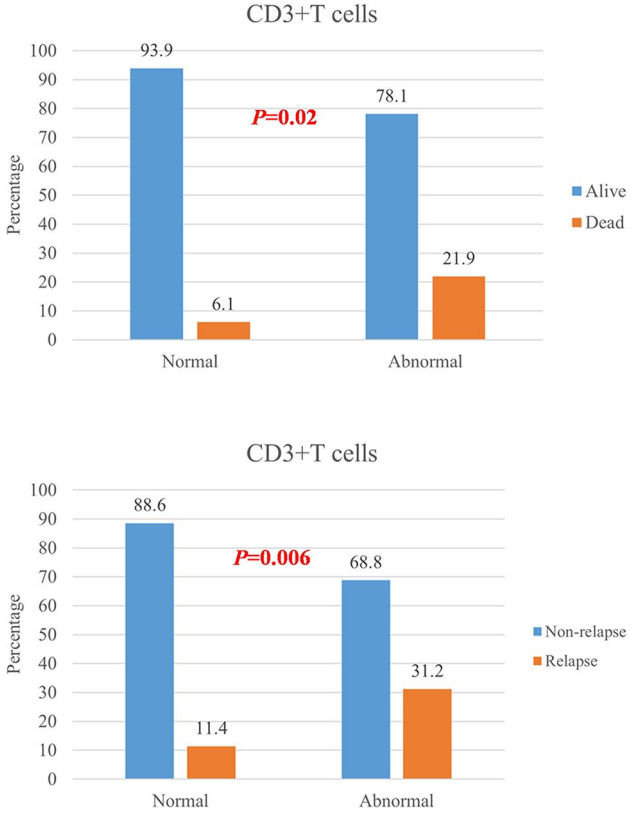

Fig. 1 Effect of abnormal CD3+T cell numbers (outside the reference range) on prognosis

The study has revealed that levels of CD4+T cells ($P=0.003$) and CD4/CD8 ($P<0.001$) were obviously higher in children with LR group compared to the IR group at the end of chemotherapy, whereas NK cells were significantly lower in LR group ($P<0.001$). Furthermore, B cells ($P=0.002$), IgG ($P=0.008$), and IgM ($P=0.007$) levels were significantly higher in LR group compared to IR group. Evaluation of bone marrow remission status was conducted on day 46 after initiation of chemotherapy, and incomplete remission at this time point indicated poor prognosis. The study demonstrated that on day 46, the levels of IgA ($P=0.012$) and IgG ($P=0.032$) in patients without complete remission were notably lower compared to those in patients who achieved complete remission (Table 3).

In addition, NK cells, T-cell compartment (CD3+T cells, CD4+T cells, CD8+T cells, and CD4/CD8 ratio), B cells, IgA, IgG, and IgM experienced a significant decrease following the completion of chemotherapy, with B cells showing the most pronounced reduction ($P<0.001$, Figs. 2 and 3).

Within 6 months after completion of treatment, 17 cases had repeated infections, with respiratory tract infections being the most common, and no serious infections occurred. The study discovered that there was no statistically significant difference in the incidence of infection in patients with decreased B cells, CD3+T cells, NK cells, IgM, IgG and CD4/CD8 compared to normal patients ($P>0.05$, see supplementary Table 3).

Analysis of immune cells reconstruction after treatment

The study proved that the T-cell compartment substantially returned to baseline levels six months after the end of chemotherapy, with the exception of a persistent decrease in CD4/CD8 levels in 57.8% (26/45) of cases. Subsequent analysis of immune cells recovery in 38 children at the six-month mark post-chemotherapy (E3) indicated significant improvement in all indexes ($P<0.001$, Table 4) except for CD4/CD8, which did not show significant recovery ($P=0.451$) compared to the end of chemotherapy (E2).

A cohort of 30 pediatric patients diagnosed with ALL were monitored for a period of 12 months post-treatment. Among these patients, 14 cases (46.7%) exhibited a decrease in CD4/CD8 levels, while other immune parameters returned to baseline values. Our findings suggest that CD4/CD8 ratios were aberrant both pre- and post-chemotherapy. Subsequent analysis of 18 patients disclosed a further decline in CD4/CD8 ratios following chemotherapy, although these values displayed a trend towards normalization with prolonged follow-up duration (Fig. 4).

Table 3 Immune cells of ALL children with different risk and D46 remission status after chemotherapy

	Risk			D46 remission status		
	LR (*n* = 73)	**IR (*n* = 58)**	***P***	**Yes (*n* = 119)**	**No (*n* = 12)**	***P***
CD3 + T cells	1017 (656–1375)	921 (650–1259)	0.477	963 (648–1366)	931 (685–1178)	0.892
NK cells	32 (17–90)	107 (42–183)	**<0.001**	49 (23–130)	108 (37–190)	0.126
CD4 + T cells	482 (293–651)	373 (253–488)	**0.003**	422 (264–586)	431 (262–480)	0.555
CD8 + T cells	393 (287–629)	424 (279–605)	0.609	399 (281–630)	446 (316–563)	0.981
CD4/CD8	1.07 (0.86–1.47)	0.77 (0.63–1.08)	**<0.001**	0.99 (0.73–1.36)	0.90 (0.64–1.28)	0.490
B cells	17 (9–55)	8 (2–70)	**0.002**	12 (6–63)	6 (5–22)	0.156
IgA	0.46 (0.29–0.66)	0.50 (0.33–0.78)	0.411	0.47 (0.33–0.75)	0.29 (0.13–0.52)	**0.012**
IgG	6.70 (5.20–8.50)	5.40 (3.75–7.60)	**0.008**	6.10 (4.90-8.00)	4.80 (3.45–6.65)	**0.032**
IgM	0.28 (0.20–0.45)	0.21 (0.11–0.36)	**0.007**	0.27 (0.16–0.43)	0.19 (0.10–0.31)	0.088

The bold fonts describes the difference in the number of immune cells in patients with different risk levels (low risk and intermediate risk) and in remission status at the 46th day after chemotherapy

Discussion

ALL is the predominant hematological malignancy in pediatric patients, typically managed through a diverse array of chemotherapeutic agents. Prolonged administration of these medications may compromise the immune system, leading to a sustained state of immunosuppression post-treatment [21, 22]. This impediment hinders the immune system's ability to effectively combat infections and malignancies. Therefore, it is imperative to investigate alterations in immune cells in pediatric ALL patients pre- and post-chemotherapy, as well as to determine the optimal timeframe for immune cells recovery following treatment.

A total of 146 patients with ALL were included in this study, most of them were male, similar to previous studies [23]. In a British study (UKALL2003) [24], males received chemotherapy for longer, whereas in this study, males received the same chemotherapy regimen as females. This study found evidence of immune cells dysregulation in 146 children with ALL prior to chemotherapy, characterized by decreased levels of CD3 + T cells, CD4 + T cells, CD8 + T cells, and CD4/CD8 ratios. Specifically, the proportion of CD4/CD8 was significantly lower in 41 out of 146 cases (28.1%), consistent with findings from previous research [25–27]. The decline in CD4/CD8 ratios suggests compromised T-cell compartment, diminished ability to eradicate leukemic cells, and reduced antitumor efficacy. The levels of CD3 + T cells, CD4 + T cells, CD8 + T cells, CD4/CD8 ratio, and B cells were found to be significantly higher in children with B-ALL compared to those with T-ALL ($P<0.05$). Conversely, the levels of CD8 + T cells and NK cells were lower in children in LR group compared to those in IR group ($P<0.05$), suggesting varying degrees of abnormal immune cell numbers based on risk stratification. It could also be connected to recurrent cytogenetic abnormalities associated with favorable prognosis in LR group, but no pertinent research has been conducted to bolster this theory. Prior to chemotherapy, the mortality and recurrence rates were higher in the group with abnormal CD3 + T cell numbers (outside the reference range) compared to the normal group ($P<0.05$). An abnormal number of CD3 + T cells may contribute to a weakened anti-tumor response, potentially leading to a poorer prognosis. It is proposed that the number of CD3 + T cells may serve as a valuable indicator for predicting prognosis.

A significant decrease in CD4/CD8 (69/131, 52.7%) and NK cells (82/131, 62.6%) was observed following chemotherapy, suggesting that these cells may be particularly vulnerable to the effects of chemotherapy. Furthermore, a notable reduction in B cells (112/131, 85.5%) was also noted, indicating a substantial impairment of B cells post-chemotherapy. These findings are consistent with previous research [26, 28, 29], highlighting the significant impact of chemotherapy on the B cells throughout the treatment process. The study found that LR group had lower intensity of chemotherapy compared to those with IR group, leading to higher levels of B cells, CD4 + T cells, CD4/CD8, IgG, and IgM at the end of treatment, and it is consistent with previous research [30, 31]. Prior to chemotherapy initiation, LR group exhibited lower levels of NK cells compared to those with IR

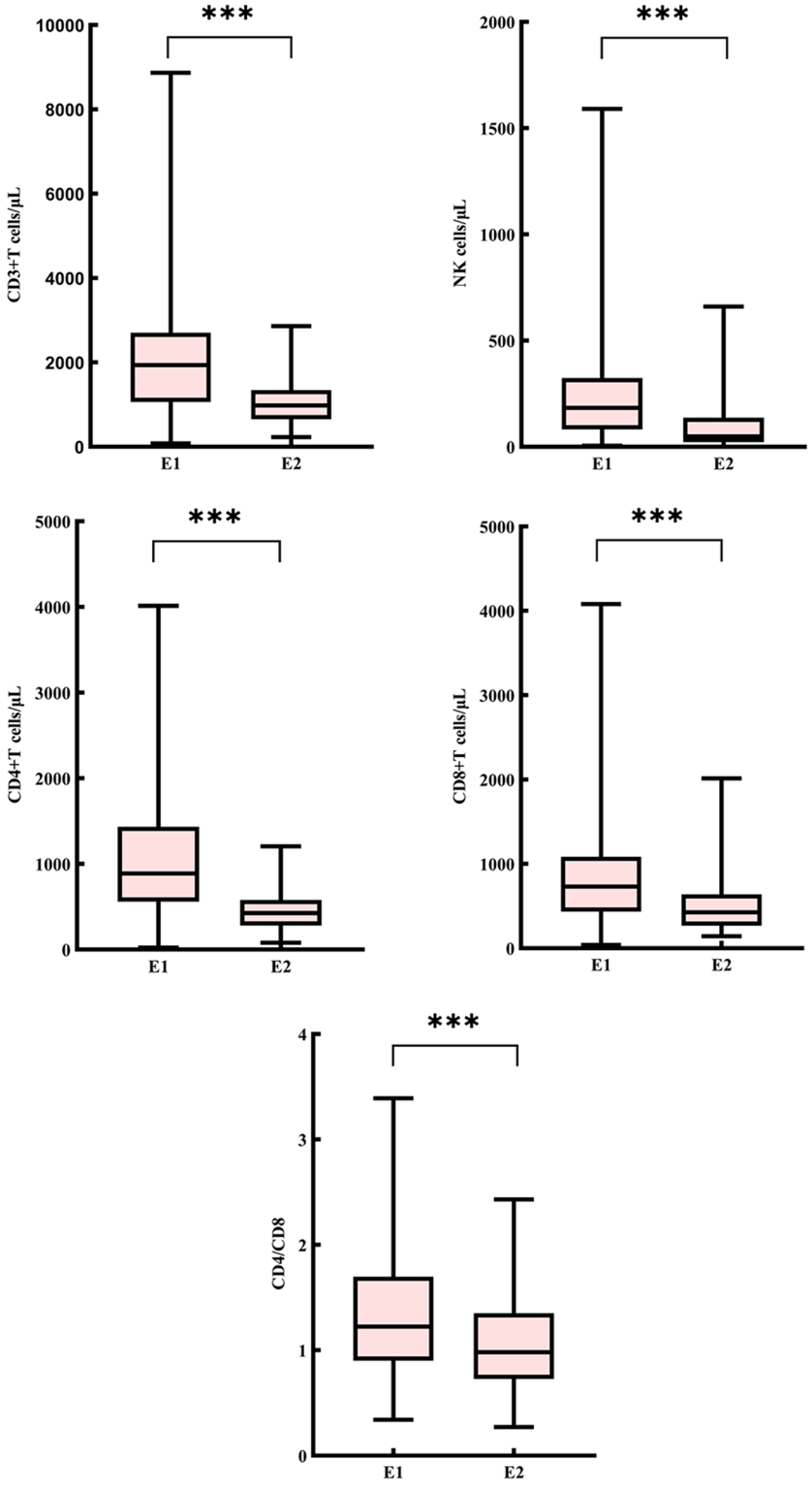

Fig. 2 Effect of chemotherapy on T-cell compartment and NK cells in 98 patients. *NotesP* value: ns, $P \geq 0.05$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$

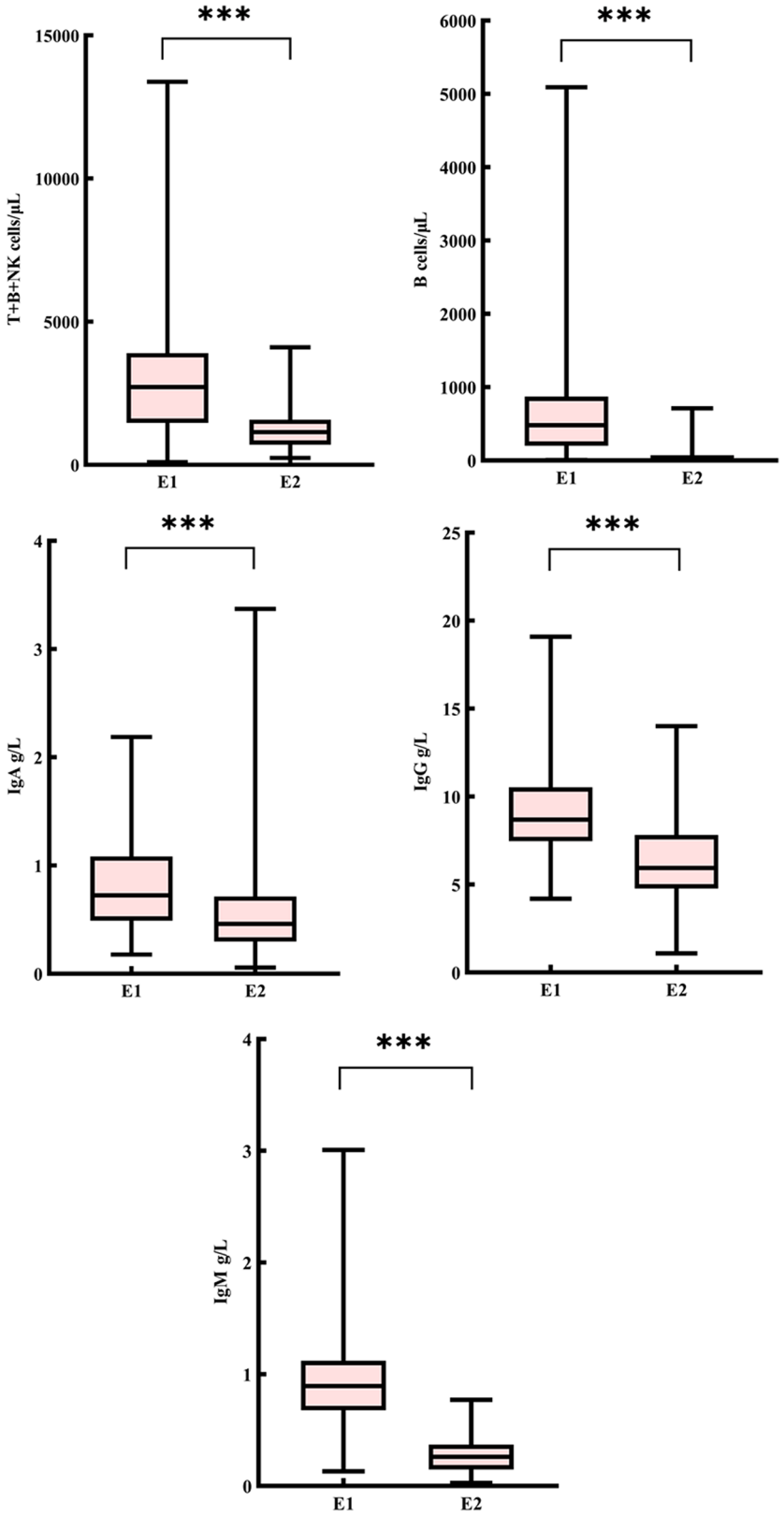

Fig. 3 Effect of chemotherapy on B cells and all immunoglobulin subclasses in 98 patients. *Notes P* value: ns, $P \geq 0.05$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$

Table 4 Analysis of immune cells reconstitution during E2 and E3 in 38 children with ALL

	E2 (*n* = 38)	E3 (*n* = 38)	*P*
CD3 + T cells	972 (658–1352)	1571 (997–2111)	<0.001
NK cells	40 (19–119)	150 (102–251)	<0.001
CD4 + T cells	425 (288–598)	728 (402–959)	<0.001
CD8 + T cells	392 (291–631)	616 (459–906)	<0.001
CD4/CD8	1.00 (0.74–1.40)	0.98 (0.76–1.31)	0.451
B cells	12 (6–38)	527 (245–718)	<0.001
IgA	0.41 (0.27–0.61)	0.73 (0.53–1.22)	<0.001
IgG	5.55 (4.40–6.77)	7.25 (6.17–8.92)	<0.001
IgM	0.24 (0.13–0.31)	0.59 (0.36–0.72)	<0.001
T + B + NK cells	1083 (767–1504)	2332 (1411–3014)	<0.001

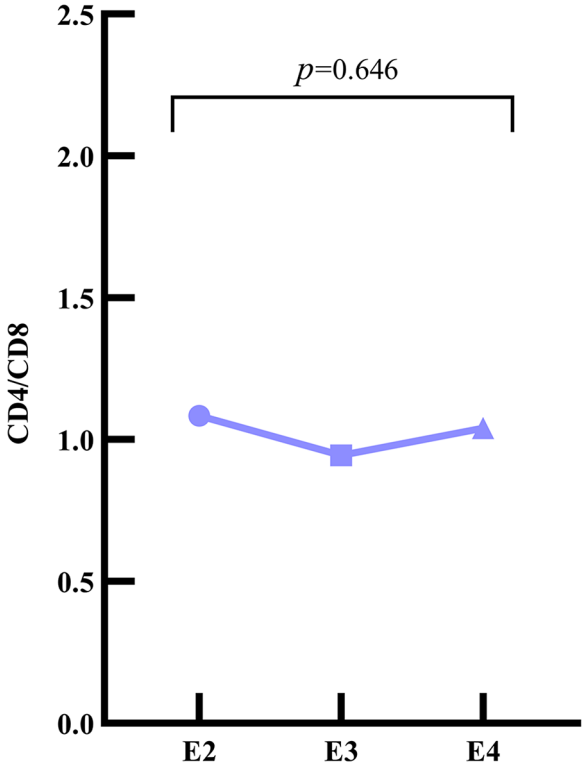

Fig. 4 Changes of CD4/CD8 in 18 patients in three different periods (E2, E3, E4)

group, and this discrepancy persisted at the end of chemotherapy ($P<0.05$). The difference in the number of NK cells between the two groups before treatment may be the main factor leading to this result. It is necessary to further expand the sample size to provide a stronger conclusion in the future.

This study observed a significant decrease in NK cells, T-cell compartment, B cells and all immunoglobulin subclasses following chemotherapy ($P<0.001$), suggesting a substantial impact of chemotherapy on the immune cells of children. Notably, B cells were found to be the most severely affected, aligning with findings from previous studies [26, 30]. Six months after the end of chemotherapy, all indexes, with the exception of CD4/CD8, exhibited significant recovery compared to post-treatment levels ($P<0.001$), in which B cells basically returned to normal. Conversely, the CD4/CD8 ratio did not demonstrate significant recovery, aligning with findings from previous studies [32–34]. Although the number of immune cells decreased sharply after treatment in children with ALL, there was no significant difference in the incidence of infection between patients with abnormal immune cells and normal patients after treatment. This may be because the study was retrospective in nature, meaning that some patients lost relevant data because they received treatment in different hospitals. Leukemia patients may be more susceptible to infections after treatment ends than the general population. A study involving 2,204 patients discovered that leukemia survivors experienced higher infection rates (RR = 1.77, 95%CI: 1.69–1.71) and noticeably higher infection-related deaths (HR = 149.3, 95%CI: 20.4-1091.9) one year after treatment concluded compared to controls [35].

Through examining the immune cells of pediatric patients diagnosed with ALL both before and after chemotherapy treatment, the study established that

chemotherapeutic agents exert a notable impact on the immune response of afflicted individuals. Specifically, high-intensity chemotherapy regimens have been found to induce substantial impairment in overall immune indexes, with B cells exhibiting the most pronounced deterioration. However, it was observed that the number of humoral immune indexes (B cells and all immunoglobulin subclasses) recovered at a faster rate compared to the T-cell compartment following the end of chemotherapy. The examination of immune cells throughout and following leukemia treatment can offer valuable insights for clinical practice. In cases where immune reconstruction is compromised and prolonged immunodeficiency is present, interventions to enhance immunity may be necessary to mitigate the risk of severe infections. The degree of immune dysfunction in children with ALL may serve as a prognostic indicator, aiding in clinical risk stratification.

Conclusions

Acute lymphoblastic leukemia is a prevalent hematological malignancy in pediatric patients, with chemotherapy serving as the primary therapeutic modality. While chemotherapeutic agents effectively induce tumor cell apoptosis, they also elicit collateral damage to healthy immune cells, leading to significant impairment of the host immune barrier and prolonged immunodeficiency. After the completion of chemotherapy, the B cells experienced the most severe impairment, but recovered rapidly and ultimately returned to baseline levels within 6 months post-treatment. In contrast, the CD4/CD8 levels did not return to normal after 12 months of treatment, consequently impacting the T lymphocyte levels. Prior to treatment, patients with abnormal CD3+T cells were found to have elevated risks of mortality and recurrence compared to those with normal levels, indicating the potential utility of this index in prognostic assessments.

Abbreviations

ALL	Acute lymphoblastic leukemia
LR	Low risk
IR	Intermediate risk
HR	High risk
Ig	Immunoglobulin
NK	Natural killer
M	Median
IQR	Interquartile range
MRD	Minimal residual disease
BMI	Body mass index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-05030-4.

Supplementary Material 1: (supplementary file)

Supplementary Material 2: (supplementary tables)

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Author contributions

QH designed the study. YX performed the data collection and statistical analysis. AZ and AL supervised the project. YX wrote the original draft. QH was responsible for the revision of the manuscript. All authors read and approved the manuscript.

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Data availability

All primary data are included in this article and additional data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology (reference no. 2020-S207), China, in accordance with the declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. Cancer J Clin. 2023;73(1):17–48.
2. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. Cancer J Clin. 2014;64(2):83–103.
3. Pui CH, Behm FG, Crist WM. Clinical and biologic relevance of immunologic marker studies in childhood acute lymphoblastic leukemia. Blood. 1993;82(2):343–62.
4. Svendsen AL, Feychting M, Klaeboe L, Langmark F, Schüz J. Time trends in the incidence of acute lymphoblastic leukemia among children 1976–2002: a population-based nordic study. J Pediatr. 2007;151(5):548–50.
5. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001–2007. Blood. 2012;119(1):34–43.
6. LeBien TW, Tedder TF. B lymphocytes: how they develop and function. Blood. 2008;112(5):1570–80.
7. Hayakawa K, Li YS, Wasserman R, Sauder S, Shinton S, Hardy RR. B lymphocyte developmental lineages. Ann N Y Acad Sci. 1997;815:15–29.
8. Eibel H, Kraus H, Sic H, Kienzler AK, Rizzi M. B cell biology: an overview. Curr Allergy Asthma Rep. 2014;14(5):434.
9. Tedder TF, Zhou LJ, Engel P. The CD19/CD21 signal transduction complex of B lymphocytes. Immunol Today. 1994;15(9):437–42.
10. Zheng XH, Zhang XY, Dong QQ, Chen F, Yang SB, Li WB. Efficacy and safety of chimeric antigen receptor-T cells in the treatment of B cell lymphoma: a systematic review and meta-analysis. Chin Med J. 2020;133(1):74–85.
11. Jasinski S, De Los Reyes FA, Yametti GC, Pierro J, Raetz E, Carroll WL. Immunotherapy in Pediatric B-Cell Acute Lymphoblastic Leukemia: advances and Ongoing challenges. Paediatr Drugs. 2020;22(5):485–99.
12. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. Immunol Today. 1994;15(9):450–4.
13. Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. Curr Dir Autoimmun. 2005;8:140–74.

14. Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms. Blood. 2008;111(8):3941–67.
15. Khummuang S, Chuensirikulchai K, Pata S, Laopajon W, Chruewkamlow N, Mahasongkram K, et al. Characterization and functional analysis of novel circulating NK cell sub-populations. Int Immunol. 2019;31(8):515–30.
16. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, et al. Innate or adaptive immunity? The example of natural killer cells. Sci (New York NY). 2011;331(6013):44–9.
17. Lauzon NM, Mian F, MacKenzie R, Ashkar AA. The direct effects of toll-like receptor ligands on human NK cell cytokine production and cytotoxicity. Cell Immunol. 2006;241(2):102–12.
18. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncology: Official J Am Soc Clin Oncol. 2012;30(14):1663–9.
19. Pui CH. Precision medicine in acute lymphoblastic leukemia. Front Med. 2020;14(6):689–700.
20. Brown P, Inaba H, Annesley C, Beck J, Colace S, Dallas M, et al. Pediatric Acute Lymphoblastic Leukemia, Version 2.2020, NCCN Clinical Practice guidelines in Oncology. J Natl Compr Cancer Network: JNCCN. 2020;18(1):81–112.
21. Kosmidis S, Baka M, Bouhoutsou D, Doganis D, Kallergi C, Douladiris N, et al. Longitudinal assessment of immunological status and rate of immune recovery following treatment in children with ALL. Pediatr Blood Cancer. 2008;50(3):528–32.
22. Mazur B, Szczepański T, Karpe J, Sońta-Jakimczyk D, Bubała H, Torbus M. Decreased numbers of CD4 + T lymphocytes in peripheral blood after treatment of childhood acute lymphoblastic leukemia. Leuk Res. 2006;30(1):33–6.
23. Tang J, Yu J, Cai J, Zhang L, Hu S, Gao J, et al. Prognostic factors for CNS control in children with acute lymphoblastic leukemia treated without cranial irradiation. Blood. 2021;138(4):331–43.
24. Vora A, Goulden N, Mitchell C, Hancock J, Hough R, Rowntree C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2014;15(8):809–18.
25. Milosević DB. The different level of immunological recovery after chemotherapy in leukemia and lymphoma patients. J Experimental Clin cancer Research: CR. 2001;20(4):517–22.
26. Eyrich M, Wiegering V, Lim A, Schrauder A, Winkler B, Schlegel PG. Immune function in children under chemotherapy for standard risk acute lymphoblastic leukaemia - a prospective study of 20 paediatric patients. Br J Haematol. 2009;147(3):360–70.
27. Hitzig WH, Plüss HJ, Joller P, Pilgrim U, Tacier-Eugster H, Jakob M. Studies on the immune status of children with acute lymphocytic leukaemia. I. Early phase before and after first remission. Clin Exp Immunol. 1976;26(3):403–13.
28. Koskenvuo M, Ekman I, Saha E, Salokannel E, Matomäki J, Ilonen J, et al. Immunological reconstitution in children after completing Conventional Chemotherapy of Acute Lymphoblastic Leukemia is marked by impaired B-cell compartment. Pediatr Blood Cancer. 2016;63(9):1653–6.
29. Wiegering V, Frank J, Freudenberg S, Morbach H, Schlegel PG, Eyrich M, et al. Impaired B-cell reconstitution in children after chemotherapy for standard or medium risk acute precursor B-lymphoblastic leukemia. Leuk Lymphoma. 2014;55(4):870–5.
30. van Tilburg CM, van der Velden VH, Sanders EA, Wolfs TF, Gaiser JF, de Haas V, et al. Reduced versus intensive chemotherapy for childhood acute lymphoblastic leukemia: impact on lymphocyte compartment composition. Leuk Res. 2011;35(4):484–91.
31. Ek T, Josefson M, Abrahamsson J. Multivariate analysis of the relation between immune dysfunction and treatment intensity in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2011;56(7):1078–87.
32. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood B-lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukemia. Cancer. 1992;69(6):1481–6.
33. Alanko S, Salmi TT, Pelliniemi TT. Recovery of natural killer cells after chemotherapy for childhood acute lymphoblastic leukemia and solid tumors. Med Pediatr Oncol. 1995;24(6):373–8.
34. Alanko S, Salmi TT, Pelliniemi TT. Recovery of blood T-cell subsets after chemotherapy for childhood acute lymphoblastic leukemia. Pediatr Hematol Oncol. 1994;11(3):281–92.
35. Pelland-Marcotte MC, Pole JD, Hwee J, Sutradhar R, Science M, Nathan PC, et al. Long-term risk of infections after treatment of Childhood Leukemia: a Population-based Cohort Study using Administrative Health data. J Clin Oncology: Official J Am Soc Clin Oncol. 2019;37(29):2651–60.

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