Heliyon 10 (2024) e27305

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Effect of rituximab on immune status in children with aggressive mature B-cell lymphoma/leukemia–a prospective study from CCCG-BNHL-2015

Jiajia Dong [a], Zhou Xu [b], Xia Guo [c], Fanghua Ye [a], Chenying Fan [a], Ju Gao [c], Yijin Gao [b], Liangchun Yang [a,*]

[a] Department of Pediatrics, Xiangya Hospital Central South University, Changsha, China
[b] Department of Hematology/Oncology, School of Medicine, Shanghai Children's Medical Center, Shanghai Jiaotong University, Shanghai, China
[c] Department of Pediatrics, Key Laboratory of Birth Defects and Related Disease of Women and Children, Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China

ARTICLE INFO

Keywords:
Rituximab
Mature B-Cell lymphoma
Immune status
Side effect
Pediatrics

ABSTRACT

Background: Limited research has been conducted on the impact of rituximab on immune function and the incidence of side effects in children undergoing combination chemotherapy for aggressive mature B-cell lymphoma/leukemia.

Methods: Clinical data from 85 patients with primary pediatric aggressive mature B-cell lymphoma/leukemia, treated according to the Chinese Children's Cancer Group (CCCG)-mature B-cell non-Hodgkin lymphoma (BNHL)-2015 protocol from June 1, 2015, to December 1, 2022, were collected from three tertiary medical centers in China. Patients with pre-existing malignancies or primary immune deficiencies (PIDs) were excluded.

Results: Between June 1, 2015, and December 1, 2022, 85 patients (65 [76.5%] boys and 20 [23.5%] girls; mean age, 6.95 years) were enrolled, and immune data at baseline during follow-up were analyzed. At the end of chemotherapy, a higher proportion of patients in the R4 group exhibited a decrease in peripheral blood $CD3^{-}$ $CD19^{+}$ B cells (20[100%] of 20 vs 13[47.8%] of 18, $p = 0.04$), $CD3^{+}$ T cells (21[91.3%] of 23 vs 14[60.9%] of 23, $p = 0.016$), and serum IgM (14 [60.9%] of 23 vs 4[17.4%] of 23, $p = 0.003$) compared to the R3 group. However, these differences were no longer statistically significant six months after chemotherapy administration. The combination of rituximab with AA was associated with a higher incidence of significant thrombocytopenia (49[81.7%] of 60 vs 29[52.7%] of 55, $p = 0.001$) and infection (35[58.3%] of 60 vs 17[30.9%] of 55, $p = 0.003$) compared to AA alone. Furthermore, the combination of rituximab with BB was linked to a higher incidence of significant thrombocytopenia (32[52.5%] of 61 vs 31[31.0%] of 100, $p = 0.007$) compared to BB alone.

Conclusions: While the effects of rituximab in combination with intense chemotherapy for childhood aggressive mature B-cell lymphoma/leukemia on children's immune function generally recovers within six months it may still prolong the recovery from immunoglobulinemia, posing a risk of secondary infections. Further studies are required to identify children with potential primary immunodeficiencies.

* Corresponding author.
E-mail address: 405010@csu.edu.cn (L. Yang).

https://doi.org/10.1016/j.heliyon.2024.e27305
Received 28 September 2023; Received in revised form 27 February 2024; Accepted 27 February 2024
Available online 5 March 2024

1. Introduction

Rituximab is a first-generation anti-CD20 monoclonal antibody [1]. Since its approval for clinical use more than 20 years ago, it has rapidly become a cornerstone for the treatment of CD20-positive malignancies [2,3]. While therapies harnessing the immune system have transformed the treatment landscape for many diseases, they may also pose risks and give rise to adverse secondary events. The main adverse effects of rituximab include infusion-related events, hematological events, and cardiovascular events, but there are few reports on its toxicity and immune system inhibition after combination with intense chemotherapy [3,4]. Therefore, the possible advantages of rituximab need to be weighed against the potential risks of unforeseen and serious adverse reactions.

The Chinese Children's Cancer Group (CCCG)-mature B-cell non-Hodgkin lymphoma (BNHL)-2015 (CCCG-BNHL-2015) study marked the first prospective multi-institutional investigation conducted by the CCCG lymphoma group. The protocol increased the 4-year event-free survival (EFS) of pediatric patients with aggressive mature B-cell non-Hodgkin lymphoma/leukemia (B-NHL/B-AL) from 76% to 88.3% [5]. A pre-specified secondary objective of the CCCG-BNHL-2015 protocol was to evaluate the toxicity profile associated with the addition of rituximab and to appraise its feasibility in the setting of a developing country. To assess the safety of rituximab combined with intensive chemotherapy for treating invasive mature B-cell lymphoma in children, we prospectively summarized and analyzed clinical data from children with invasive mature B-cell lymphoma initially treated at three tertiary medical centers in China.

This study aimed to examine the effects of adding rituximab to intensive chemotherapy on immune reconstitution after active treatment. Research gaps exist in the identification of children and adolescents who may benefit from immunoglobulin replacement therapy and revaccination. Our results provide new data to help fill this gap, particularly in justifying the use of rituximab in developing countries [6].

2. Methods

2.1. Patients

From June 1, 2015, to December 1, 2022, children and adolescents with primary aggressive mature B-cell lymphoma/leukemia with a pathological or cytological diagnosis who attended the Department of Hematology/Oncology of the Shanghai Children's Medical Centre, the Department of Pediatrics of Xiangya Hospital of Central South University and the Department of Pediatrics of the Second Hospital of West China of Sichuan University were treated according to the China Children's Cancer Group (CCCG) BNHL-2015 protocol. The exclusion criteria were the absence of congenital immune disease, no history of organ transplantation, and no secondary tumor. General clinical and immune data on the child should be available.

The study was approved by the Medical Ethics Committee of Shanghai Children's Medical Center (SCMCIRB-J2014004). We also officially registered it on the International Clinical Trials website (ClinicalTrials.gov ID: NCT02405676). The guardians of the children have also provided their signed consent.

Tumor biopsies and cytological, immunological, and genetic examinations were performed to diagnose B-NHL/B-AL. NHL subtypes were classified according to the 2008 WHO classification of lymphomas [7]. Clinical staging was performed using the St. Jude/Murphy staging criteria [8]. Patients meeting the stage IV diagnostic criteria, involving central and/or bone marrow infiltration and a proportion of bone marrow-naïve cells of >30%, were categorized into the mature B-cell leukemia group. The patients were classified into R1, R2, R3, and R4 groups according to their clinical stage and pretreatment serum lactate dehydrogenase (LDH) levels. Group R1 included completely resected stages I and II; group R2 included incompletely resected stages I and II with LDH less than two times the upper limit of the normal value; group R3 included stage III with LDH less than four times the normal value; stage I/II with LDH more than two times the normal value; and less than four times of the normal value; group R4 included stage III with LDH more than four times the normal value, and all stage IV and leukemia stages. Children in group R4 were treated with a single dose of rituximab (375 mg/m^2) before the 2nd, 3rd, 4th, and 5th courses of chemotherapy in group R3. The therapeutic framework of each group was as follows: Group R1 had three courses of treatment, alternating between regimens A and B; Group R2 had five courses of treatment, alternating between regimens A and B; Group R3 had six courses of treatment, with regimen P + A for the first course of treatment, followed by BB and AA regimens alternately (P + A-BB-AA-BB-AA-BB); and group R4 had six courses of treatment, with the addition of one dose of rituximab to the regimen of Group R3 from the second course of treatment onwards (P + A-RBB-RAA-RBB-RAA-BB). Specific programs have been published previously [5]. The specific chemotherapy regimens are listed in Table S1.

2.2. Procedures

An enzyme-linked immunosorbent assay (ELISA) was used to determine serum immunoglobulin levels (IgG, IgM, and IgA), and flow cytometric counts of peripheral blood T, B, and natural killer (NK) cell subsets and/or absolute values were performed at baseline, at the end of chemotherapy, and every 6 months thereafter. The normal reference values for lymphocyte subset counts and serum immunoglobulin levels are listed in Tables S2–S5. After each course of treatment and before the next course, the National Cancer Institute's (NCI) Treatment-Related Adverse Events (TRAE) scale was used to score serious adverse events, and a score of more than 3 was considered a criterion for serious adverse events.

2.3. Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM SPSS, 2017). Count data were expressed as percentages and numbers of cases using the $\chi 2$ test. All comparisons were two-sided, and p-values <0.05 were considered statistically significant.

3. Results

3.1. Clinical characteristics of patients

Between January 1, 2015, and December 1, 2022, 85 children who met the enrollment requirements and received chemotherapy according to the regimen at three Chinese tertiary care centers were enrolled. Forty-one children were classified into group R3 and received intensified chemotherapy, whereas 44 children were classified into group R4 and received intensified chemotherapy and four doses of rituximab.

The baseline characteristics of the 85 patients are presented in Table 1. The children included in this study had an average age of 6.95 years at the time of diagnosis. A total of 65 boys and 20 girls, with a male-to-female ratio of 3.25:1, were included in the study. The pathological types included Burkitt's lymphoma in 49 cases (57.6%), diffuse large B-cell lymphoma in 11 cases (12.9%), other high-grade B-cell lymphomas in 15 cases (17.6%), and mature B-cell acute leukemia in 10 cases (11.8%).

3.2. Lymphocytes after the end of chemotherapy

The recovery of peripheral blood immune cells in children at the end of chemotherapy is shown in Table 2. The lymphocyte count ranges are listed in Table S7. At the end of chemotherapy, the total peripheral blood lymphocyte count of most patients was below normal (33 [76.7%] of 43 patients vs. 35 [87.5%] of 40 patients). We gathered immune function indices from laboratory tests conducted at the conclusion of chemotherapy for 46 children (23 in the R3 group and 23 in the R4 group). Notably, $CD3^{-}CD19^{+}$ B cells showed a decrease in 13 out of 18 (72.2%) cases in the R3 group and 20 out of 20 (100%) cases in the R4 group, indicating a statistically significant difference ($p = 0.04$). Additionally, $CD3^{+}$ T cell counts decreased in both groups, but the proportions exhibited a significant difference (91.3% vs. 60.9%, $p = 0.016$). Low $CD3^{-}CD56^{+}$ NK cells counts were presented in 12(60.0%) of 20 patients who received chemotherapy versus 8 (44.4%) of 18 who received chemotherapy with rituximab, while the difference was not statistically significant ($p = 0.338$).

Six months after the end of chemotherapy, we collected information on the immune cell counts of 37 children (18 in the R3 group and 19 in the R4 group). Lymphocyte counts rebounded in both groups of children; however, interestingly, the total peripheral blood lymphocyte counts were lower (R3 vs. R4, 27.0% vs. 38.9%, $p = 0.281$). Except for $CD3^{-}CD56^{+}$ NK cells (R3 vs. R4, 23.1% vs. 70.6%, $p = 0.01$), the percentage decline in each immune cell count was not significantly different between the two groups. One (7.7%) of 13 children from the R3 group and 5 (29.4%) of 17 children from the R4 group still had low $CD3^{-}CD19^{+}$ B cell counts, but the difference

Table 1
Patient clinical and laboratory characteristics at baseline.

Characteristics	All patients	R3	R4
Number of patients	85	44(51.8%)	41(48.2%)
Age(range),years	6.95(2–13)	6.95(2–13)	7.11(2–13)
Median age in years	6	7	6
<5	33(38.8%)	16(18.8%)	17(41.5%)
5~10	37(43.5%)	22(25.9%)	15(36.6%)
>10	15(17.6%)	6(13.6%)	9(22.0%)
Gender			
Male	65(76.5%)	36(81.8%)	29(70.7%)
Female	20(23.5%)	8(18.1%)	12(29.3%)
Pathological diagnosis			
Burkitt lymphoma	49(57.6%)	32(72.7%)	17(41.5%)
Diffuse large B-cell lymphoma	11(12.9%)	5(11.4%)	6(14.6%)
High-grade mature B-cell lymphoma, NOS	15(17.6)	7(15.9%)	8(19.5%)
mature B-cell acute leukemia	10(11.8%)	/	10(24.4%)
St Jude stage			
Stage II	3(3.5%)	3(6.8%)	/
Stage III	63(74.1%)	41(93.2%)	22(53.7%)
Stage IV	13(15.3%)	/	13(31.7%)
Leukemia presentation (mature B-cell acute leukemia)	6(7.1%)	/	6(14.6%)
LDH			
<2 N	44(51.8%)	36(81.8%)	8(19.5%)
2–4 N	14(16.5%)	8(18.2%)	6(14.6%)
>4 N	27(31.8%)	/	27(65.9%)
Bone marrow involvement	17(2.9%)	/	17(41.5%)
CNS involvement	7(8.2%)	/	7(17.1%)

NOS, not otherwise specified.

Table 2
Lymphocytes after the end of chemotherapy.

	the end of chemotherapy			6 months after the end of chemotherapy			1 year after the end of chemotherapy			2 years after the end of chemotherapy			3 years after the end of chemotherapy		
	R3	R4	P Value	R3	R4	P Value	R3	R4	P Value	R3	R4	P Value	R3	R4	P Value
Total lymphocytes	43	40		37	36		39	37		25	29		18	21	
Low	33 (76.7%)	35 (87.5%)	0.203	10 (27.0%)	14 (38.9%)	0.281	2(5.1%)	2(5.4%)	>0.999	2(8%)	2(6.9%)	>0.999	0(0%)	1(4.8%)	>0.999
$CD3^+$ T cells	23	23		18	19		31	34		13	20		9	9	
Low	14 (60.9%)	21 (91.3%)	0.016	2(11.1%)	4(21.1%)	0.709	3(9.7%)	3(8.8%)	>0.999	3 (23.1%)	2 (10.0%)	0.598	1 (11.1%)	1 (11.1%)	>0.999
$CD3^+$ $CD4^+$ cells	23	23		18	19		31	34		13	20		9	9	
Low	20 (87.0%)	21 (91.3%)	>0.999	4(22.2%)	6(31.6%)	0.787	4(12.9%)	3(8.8%)	0.897	3 (23.1%)	3 (15.0%)	0.900	2 (22.2%)	2 (22.2%)	>0.999
$CD3^+$ $CD8^+$ cells	23	23		18	19		31	34		13	20		9	9	
Low	11 (47.8%)	17 (73.9%)	0.070	3(16.7%)	3(15.8%)	>0.999	1(3.2%)	4(11.8%)	0.410	1(7.7%)	1(5.0%)	>0.999	0(0%)	1 (11.1%)	>0.999
$CD3^-CD19^+$ B cells	18	20		13	17		29	35		12	19		9	10	
Low	13 (72.2%)	20(100%)	0.040	1(7.7%)	5(29.4%)	0.311	0(0.0%)	2(5.7%)	0.497	0(0.0%)	1(5.3%)	>0.999	1 (11.1%)	1(10%)	>0.999
$CD3^-CD56^+$ NK cells	18	20		13	17		29	34		12	18		9	9	
Low	8(44.4%)	12 (60.0%)	0.338	3(23.1%)	12 (70.6%)	0.010	12 (41.4%)	13 (38.2%)	0.799	4 (33.3%)	7 (38.9%)	>0.999	2 (22.2%)	5 (55.6%)	0.335

Table 3
Immunoglobulins after the end of chemotherapy.

	the end of chemotherapy			6 months after the end of chemotherapy			1 year after the end of chemotherapy			2 years after the end of chemotherapy			3 years after the end of chemotherapy		
	R3	R4	P Value	R3	R4	P Value	R3	R4	P Value	R3	R4	P Value	R3	R4	P Value
IgA	23	23		17	15		28	31		11	19		10	13	
Low	2(8.7%)	4(17.4%)	0.662	1(5.9%)	5(33.3%)	0.076	3(10.7%)	17(54.8%)	<0.001	2(18.2%)	10(52.6%)	0.142	1(10%)	11(84.6%)	0.001
IgM	23	23		17	18		28	31		11	20		10	13	
Low	4(17.4%)	14(60.9%)	0.003	0(0.0%)	2(11.1%)	0.486	0(0.0%)	3(9.7%)	0.273	0(0.0%)	1(5.0%)	>0.999	0(0.0%)	2(15.4%)	0.486
IgG	23	23		17	18		28	31		11	20		10	13	
Low	6(26.1%)	10(43.5%)	0.216	0(0.0%)	12(66.7%)	<0.001	1(3.6%)	6(19.4%)	0.142	0(0.0%)	5(25.0%)	0.193	0(0.0%)	4(30.8%)	0.169

was not statistically significant (p = 0.311).

One year after the end of chemotherapy, we collected information on the immune cell counts of 65 children by which time most of the children's immune cell counts had returned to normal values, with no statistically significant differences between the two groups. The B-cell counts of 29 children in the R3 group returned to normal, whereas the values of two of the 35 children in the R4 group (one of whom only had data on his B-cell counts) were still lower than normal values. Two years after the completion of chemotherapy, we collected information on the immune cell counts of 13 children in the R3 group and 20 children in the R4 group. At this time, there were still individual children whose immune cell counts did not reach normal values, and some of them had not recovered to the normal level three years after the end of chemotherapy, which suggests that these children may suffer from a combination of primary immunodeficiencies.

3.3. Immunoglobulins after the end of chemotherapy

The addition of Rituximab may have a significant effect on the decrease in immunoglobulin counts of children (Table 3). At the end of chemotherapy, 4 (17.4%) of 23 children in the R3 group versus 14 (60.9%) of 23 children in the R4 group had a low IgM concentration p = 0.003, which is a statistically significant difference. The IgM values of the children in both groups almost normalized 6 months after the end of chemotherapy.

Six months after the end of treatment, none (0 of 17) of the R3 group had low IgG concentrations, whereas 12 (66.7%) of 18 children in the R4 group had low IgG concentrations (p < 0.001). One year after the end of chemotherapy, there were still 1 (3.6%) of 28 children in group R3 and 6 (19.4%) of 31 children in group R4 whose IgG concentrations did not return to normal values, and 4 (30.8%) of 13 children in group R4 still did not have normal IgG values at 3 years after the end of chemotherapy.

From 1 year after the end of treatment to 3 years after the end of treatment, there were still some children with IgA concentration below normal, and children in the R4 group were more inclined to have low IgA values. The ranges of immunoglobulin levels after chemotherapy are summarized in Table S6.

3.4. Incidence of severe adverse reactions after chemotherapy

To investigate the adverse effects of rituximab addition, we determined the incidence of the four main adverse effects (neutropenia, thrombocytopenia, mucositis and infection) after the R-AA/AA or R–BB/BB regimens and rated them according to the adverse effect rating scale, with 55 cases recorded for the AA regimen, 60 cases for the R-AA regimen, 100 cases were recorded for the BB regimen, 61 cases for the R–BB regimen (Tables 4 and 5).

Children treated with rituximab were more likely to develop grade 3 or higher thrombocytopenia and infection. The incidence of thrombocytopenia after AA vs. R-AA was 52.7% vs. 81.7% (p = 0.001), and the incidence of infection after AA vs. R-AA was 30.9% vs. 58.3% (p = 0.003). The incidence of thrombocytopenia after BB and R–BB was 31.0% and 52.5%, respectively (p = 0.007).

4. Discussion

This study revealed that the gap in B-cell lymphopenia between the groups receiving chemotherapy alone and those receiving chemotherapy with rituximab significantly narrowed 6 months after the treatment's conclusion. However, children who received rituximab were more prone to maintaining persistently low immunoglobulin concentrations and had a higher risk of experiencing grade 3 or higher thrombocytopenia and infections. The limited compliance with the follow-up data submission restricted extended analyses, relying on small sample size.

Rituximab depletes $CD20^+$ B cells [9]. CD20 is present in all B-lineage hematopoietic cells except for the earliest precursor cells, pre-B cells, and terminally differentiated antibody-producing plasma cells [10]. While the loss of $CD20^+$ B-cells from rituximab does not directly affect plasma cells, this exposure has been linked to transient B-cell depletion in the circulation. Several patients develop long-term hypogammaglobulinemia owing to this exposure [2,11,12]. In our study, some children receiving rituximab combination chemotherapy continued to have hypogammaglobulinemia even three years after the end of chemotherapy.

Children with primary immunodeficiency are at an increased risk of developing lymphoma [13]. Primary immunodeficiencies (PIDs) are a heterogeneous group of congenital disorders with varying clinical and laboratory manifestations that affect the development and/or function of the immune system [14,15]. By contrast, secondary immunodeficiencies (SIDs) decrease the number and/or function of immune cells [13]. Decreased antibody levels due to extrinsic factors, such as underlying diseases or side effects of certain drugs used to treat hematologic malignancies, are the most common types of SID. However, immunodeficiency is associated with a high risk of cancer development [16]. According to registry studies, patients with PID have a 1.4- to 5-fold increased risk of

Table 4
Incidence of severe adverse reactions after received protocol AA or R-AA.

	n	neutropenia(%)	thrombocytopenia(%)	mucositis(%)	infection(%)
AA	55	54(98.2%)	29(52.7%)	0(0.0%)	17(30.9%)
R-AA	60	60(100%)	49(81.7%)	2(3.3%)	35(58.3%)
P Value		0.478	0.001	0.514	0.003

AA, AA regimen in the CCCG-BNHL-2015 protocol; R-AA, R-AA regimen in the CCCG-BNHL-2015 protocol.

Table 5
Incidence of severe adverse reactions after chemotherapy received protocol BB or R–BB.

	n	neutropenia(%)	thrombocytopenia(%)	mucositis(%)	infection(%)
BB	100	96(96.0%)	31(31.0%)	30(30.0%)	62(65.2%)
R–BB	61	60(98.4%)	32(52.5%)	19(31.1%)	43(70.5%)
P Value		0.402	0.007	0.878	0.272

BB, BB regimen in the CCCG-BNHL-2015 protocol; R–BB, R–BB regimen in the CCCG-BNHL-2015 protocol.

developing cancer compared with the general population [17,18]. Paradoxically, SID, initially diagnosed as a result of extrinsic factors, may be partly attributed to the underlying PID. Therefore, in this era of immunomodulatory biologics, it is important to distinguish between primary and secondary defects. In the clinical setting, it may be difficult to determine the relationship between PID, SID, and hematological malignancies or autoimmunity [19]. Susceptibility to infections, as well as evidence of long-term autoimmune disease and immune dysregulation, may indicate PID. Among patients diagnosed with lymphoma, the actual prevalence of primary immunodeficiency remains unknown [20]. Although congenital immunodeficiency was an exclusion criterion in the CCCG-BNHL-2015 trial, a small number of patients in our study had an undiagnosed primary immunodeficiency. In our study, some children still had hypoimmunoglobulinemia or lymphopenia 1 year after the end of chemotherapy. It is worth exploring whether these children have combined primary immunodeficiency, and identifying these children before chemotherapy is a current therapeutic challenge. Presently, gene sequencing technologies, including next-generation sequencing (NGS) and whole exome sequencing (WES), are becoming increasingly mature. The application of these technologies may help identify children with primary immunodeficiency lymphoma before initiating chemotherapy [14,21–23].

Similar to the findings of the Inter-B-NHL Ritux 2010 trial [3], children's immune function was largely restored 1 year after the end of chemotherapy. Our study increased the data on immune function six months after the end of chemotherapy and showed that there was no statistically significant reduction in immune cell counts between the two groups; however, children treated with rituximab were more likely to have lower serum IgG levels. This finding suggests that more attention should be paid to detecting serum immunoglobulin levels in children treated with rituximab.

The COG [24] previously reported that rituximab in combination with FAB/LMB96B and C chemotherapy does not increase treatment-related toxicity. However, our study demonstrated that the addition of rituximab to the AA regimen resulted in a more pronounced decrease in platelet counts and an elevated incidence of infections when compared to the AA regimen alone. Similarly, the combination of rituximab with the BB regimen resulted in an increased incidence of infections compared to the BB regimen alone. The results of various studies suggest that the incidence of adverse reactions is highly dependent on the drug composition of the backbone regimen [4,25,26]. Although rituximab increased the adverse effects of chemotherapy, there was no increase in treatment-related deaths [5]. Taken together with the international literature, the safety of rituximab in combination with strong chemotherapy in the treatment of aggressive mature B-cell lymphoma/leukemia in children is assured [3,4,27,28].

In summary, although rituximab combination chemotherapy is relatively safe, its toxic side effects are still higher than those of chemotherapy alone; therefore, clinical indications should be strictly controlled. The need for routine supplementation with intravenous immunoglobulins (IVIG) to reduce the risk of infection at the end of treatment should be further explored in subsequent studies. The need for routine supplementation with intravenous immunoglobulins after treatment to reduce the risk of infection should be further explored in subsequent studies [29]. For children who develop hypoimmunoglobulinemia post-treatment, determining the optimal timing to initiate immunoglobulin replacement therapy, and the duration of treatment, and its effectiveness in reducing the risk of infection are critical and need close monitoring. In both adult and pediatric clinical studies involving rituximab [11,30], patients treated with IVIG have been noted to have a likelihood of developing infections, even after contributing to infections such as neutropenia, and concomitant immunosuppression. Investigators have suggested that this may be a phenomenon of reverse causation, whereby patients at higher risk for infection are more likely to receive IVIG. A randomized clinical trial examining the effect of prophylactic IVIG on the incidence of infections in children after rituximab use would provide stronger evidence.

5. Conclusion

This is the largest cohort of children at high-risk for aggressive mature B-cell lymphoma/leukemia treated with rituximab in combination with intensive chemotherapy in China. Our study revealed that while there was essentially no statistically significant difference in the impact on immune function between rituximab combined with chemotherapy and chemotherapy alone six months after treatment completion, rituximab may still delay the recovery of immunoglobulins, and its toxicity remains higher than that of chemotherapy alone. Hence, its clinical use should be carefully considered and strictly controlled. The need for routine supplementation with intravenous immunoglobulins at the end of treatment to reduce the risk of infection should be further explored in future studies. Prospective studies should be encouraged to better understand how RTX affects immune function and identify children at risk of primary immunodeficiency.

Ethics approval and consent to participate

The authors confirm that all methods were performed per the ethical standards of the Declaration of Helsinki. This study was reviewed and approved by the Medical Ethics Committee of Shanghai Children's Medical Center (approval number: [SCMCIRB-

J2014004]) and was prospectively registered on the International Clinical Trials website (ClinicalTrials.gov ID: NCT02405676). All the legal guardians of the patients provided informed consent to participate in this study. All the patients' legal guardians provided informed consent for the publication of anonymized case details.

Funding

No.

Consent for publication

Written informed consent for publication of the data was obtained from the parents of the enrolled children.

Data availability statement

The data generated in this study will not be deposited in a public database due to privacy concerns. Data supporting the findings of this study are available upon request from the corresponding author.

CRediT authorship contribution statement

Jiajia Dong: Writing – original draft, Methodology, Formal analysis, Data curation. **Zhou Xu:** Methodology, Formal analysis, Data curation. **Xia Guo:** Methodology, Formal analysis, Data curation. **Fanghua Ye:** Methodology, Formal analysis, Data curation. **Chenying Fan:** Methodology, Formal analysis, Data curation. **Ju Gao:** Writing – review & editing, Supervision. **Yijin Gao:** Writing – review & editing, Supervision, Conceptualization. **Liangchun Yang:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank all members of the Chinese Children's Cancer Group, the medical teams in each investigation center for their contributions, and all the patients and their families for their participation.

Abbreviations

PID	primary immune deficiency
EFS	event-free survival
BNHL	B-cell non-Hodgkin lymphoma
B-AL	B-cell acute leukemia
LDH	lactate dehydrogenase
ELISA	enzyme-linked immunosorbent assay
NK	natural killer
NCI	National Cancer Institute
TRAE	Treatment-Related Adverse Events
SID	secondary immune deficiency
NGS	next-generation sequencing
WES	whole exome sequencing
IVIG	intravenous immunoglobulins

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27305.

References

[1] G. Salles, M. Barrett, R. Foà, J. Maurer, S. O'Brien, N. Valente, et al., Rituximab in B-cell hematologic malignancies: a review of 20 Years of clinical experience, Adv. Ther. 34 (10) (2017) 2232–2273, https://doi.org/10.1007/s12325-017-0612-x.

[2] V. Minard-Colin, A. Aupérin, M. Pillon, G.A.A. Burke, D.A. Barkauskas, K. Wheatley, et al., Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children, N. Engl. J. Med. 382 (23) (2020) 2207–2219, https://doi.org/10.1056/NEJMoa1915315.

[3] S. Alexander, A. AupéRIN, S. Bomken, M. Csóka, B. Kazanowska, A.K. Chiang, et al., Effect of rituximab on immune status in children with mature B-cell non-Hodgkin lymphoma: a prespecified secondary analysis of the Inter-B-NHL Ritux 2010 trial, Lancet Haematol 10 (6) (2023) e445–e457, https://doi.org/10.1016/s2352-3026(23)00062-5.

[4] V. Ribrag, S. Koscielny, J. Bosq, T. Leguay, O. Casasnovas, L.M. Fornecker, et al., Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial, Lancet 387 (10036) (2016) 2402–2411, https://doi.org/10.1016/s0140-6736(15)01317-3.

[5] Y.J. Gao, Y.J. Fang, J. Gao, J. Yan, L.C. Yang, A.G. Liu, et al., A prospective multicenter study investigating rituximab combined with intensive chemotherapy in newly diagnosed pediatric patients with aggressive mature B cell non-Hodgkin lymphoma (CCCG-BNHL-2015): a report from the Chinese Children's Cancer Group, Ann. Hematol. 101 (9) (2022) 2035–2043, https://doi.org/10.1007/s00277-022-04904-w.

[6] G. Ottaviano, M. Marinoni, S. Graziani, K. Sibson, F. Barzaghi, P. Bertolini, et al., Rituximab Unveils hypogammaglobulinemia and immunodeficiency in children with autoimmune cytopenia, J. Allergy Clin. Immunol. Pract. 8 (1) (2020) 273–282, https://doi.org/10.1016/j.jaip.2019.07.032.

[7] D.A. Arber, A. Orazi, R. Hasserjian, J. Thiele, M.J. Borowitz, M.M. Le Beau, et al., The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, Blood 127 (20) (2016) 2391–2405, https://doi.org/10.1182/blood-2016-03-643544.

[8] A. Rosolen, S.L. Perkins, C.R. Pinkerton, R.P. Guillerman, J.T. Sandlund, C. Patte, et al., Revised international pediatric non-Hodgkin lymphoma staging system, J. Clin. Oncol. 33 (18) (2015) 2112–2118, https://doi.org/10.1200/jco.2014.59.7203.

[9] R. Kado, G. Sanders, W.J. Mccune, Suppression of normal immune responses after treatment with rituximab, Curr. Opin. Rheumatol. 28 (3) (2016) 251–258, https://doi.org/10.1097/bor.0000000000000272.

[10] M.J. Leandro, B-cell subpopulations in humans and their differential susceptibility to depletion with anti-CD20 monoclonal antibodies, Arthritis Res. Ther. 15 (Suppl 1) (2013) S3, https://doi.org/10.1186/ar3908.

[11] S. Barmettler, M.S. Ong, J.R. Farmer, H. Choi, J. Walter, Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia, JAMA Netw. Open 1 (7) (2018) e184169, https://doi.org/10.1001/jamanetworkopen.2018.4169.

[12] K.Y. Zhu, K.W. Song, J.M. Connors, H. Leitch, M.J. Barnett, K. Ramadan, et al., Excellent real-world outcomes of adults with Burkitt lymphoma treated with CODOX-M/IVAC plus or minus rituximab, Br. J. Haematol. 181 (6) (2018) 782–790, https://doi.org/10.1111/bjh.15262.

[13] M. Ballow, S. Sánchez-Ramón, J.E. Walter, Secondary immune deficiency and primary immune deficiency crossovers: hematological malignancies and autoimmune diseases, Front. Immunol. 13 (2022) 928062, https://doi.org/10.3389/fimmu.2022.928062.

[14] T.Y. Tan, O.J. Dillon, Z. Stark, D. Schofield, K. Alam, R. Shrestha, et al., Diagnostic impact and cost-effectiveness of whole-exome sequencing for ambulant children with suspected monogenic conditions, JAMA Pediatr. 171 (9) (2017) 855–862, https://doi.org/10.1001/jamapediatrics.2017.1755.

[15] S.G. Tangye, W. Al-Herz, A. Bousfiha, T. Chatila, C. Cunningham-Rundles, A. Etzioni, et al., Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee, J. Clin. Immunol. 40 (1) (2020) 24–64, https://doi.org/10.1007/s10875-019-00737-x.

[16] D. Verhoeven, A.J. Stoppelenburg, F. Meyer-Wentrup, M. Boes, Increased risk of hematologic malignancies in primary immunodeficiency disorders: opportunities for immunotherapy, Clin. Immunol. 190 (2018) 22–31, https://doi.org/10.1016/j.clim.2018.02.007.

[17] S. Bomken, J. Van Der Werff Ten Bosch, A. Attarbaschi, C.M. Bacon, A. Borkhardt, K. Boztug, et al., Current understanding and future research priorities in malignancy associated with inborn errors of immunity and DNA repair disorders: the perspective of an interdisciplinary working group, Front. Immunol. 9 (2018) 2912, https://doi.org/10.3389/fimmu.2018.02912.

[18] P.C. Mayor, K.H. Eng, K.L. Singel, S.I. Abrams, K. Odunsi, K.B. Moysich, et al., Cancer in primary immunodeficiency diseases: cancer incidence in the United States immune deficiency network registry, J. Allergy Clin. Immunol. 141 (3) (2018) 1028–1035, https://doi.org/10.1016/j.jaci.2017.05.024.

[19] S. Sánchez-Ramón, A. Bermúdez, L.I. González-Granado, C. Rodríguez-Gallego, A. Sastre, P. Soler-Palacín, Primary and secondary immunodeficiency diseases in oncohaematology: warning signs, diagnosis, and management, Front. Immunol. 10 (2019) 586, https://doi.org/10.3389/fimmu.2019.00586.

[20] M. Herber, P. Mertz, Y. Dieudonné, B. Guffroy, S. Jung, V. Gies, et al., Primary immunodeficiencies and lymphoma: a systematic review of literature, Leuk. Lymphoma 61 (2) (2020) 274–284, https://doi.org/10.1080/10428194.2019.1672056.

[21] C. Cifaldi, I. Brigida, F. Barzaghi, M. Zoccolillo, V. Ferradini, D. Petricone, et al., Targeted NGS platforms for genetic screening and gene discovery in primary immunodeficiencies, Front. Immunol. 10 (2019) 316, https://doi.org/10.3389/fimmu.2019.00316.

[22] M.V. Pinto, J.F. Neves, Precision medicine: the use of tailored therapy in primary immunodeficiencies, Front. Immunol. 13 (2022) 1029560, https://doi.org/10.3389/fimmu.2022.1029560.

[23] C.D. Platt, F. Zaman, W. Bainter, K. Stafstrom, A. Almutairi, M. Reigle, et al., Efficacy and economics of targeted panel versus whole-exome sequencing in 878 patients with suspected primary immunodeficiency, J. Allergy Clin. Immunol. 147 (2) (2021) 723–726, https://doi.org/10.1016/j.jaci.2020.08.022.

[24] S. Goldman, L. Smith, J.R. Anderson, S. Perkins, L. Harrison, M.B. Geyer, et al., Rituximab and FAB/LMB 96 chemotherapy in children with Stage III/IV B-cell non-Hodgkin lymphoma: a Children's Oncology Group report, Leukemia 27 (5) (2013) 1174–1177, https://doi.org/10.1038/leu.2012.255.

[25] M.A. Habibi, S. Alesaeidi, M. Zahedi, S. Hakimi Rahmani, S.M. Piri, S. Tavakolpour, The efficacy and safety of rituximab in ANCA-associated vasculitis: a systematic review, Biology 11 (12) (2022), https://doi.org/10.3390/biology11121767.

[26] V. Poeschel, G. Held, M. Ziepert, M. Witzens-Harig, H. Holte, L. Thurner, et al., Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial, Lancet 394 (10216) (2019) 2271–2281, https://doi.org/10.1016/s0140-6736(19)33008-9.

[27] J. Hochberg, J. Basso, Q. Shi, L. Klejmont, A. Flower, K. Bortfeld, et al., Risk-adapted chemoimmunotherapy using brentuximab vedotin and rituximab in children, adolescents, and young adults with newly diagnosed Hodgkin's lymphoma: a phase II, non-randomized controlled trial, J Immunother Cancer 10 (5) (2022), https://doi.org/10.1136/jitc-2021-004445.

[28] S. Lanini, A.C. Molloy, P.E. Fine, A.G. Prentice, G. Ippolito, C.C. Kibbler, Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis, BMC Med. 9 (2011) 36, https://doi.org/10.1186/1741-7015-9-36.

[29] A.M. Khojah, M.L. Miller, M.S. Klein-Gitelman, M.L. Curran, V. Hans, L.M. Pachman, et al., Rituximab-associated Hypogammaglobulinemia in pediatric patients with autoimmune diseases, Pediatr Rheumatol Online J 17 (1) (2019) 61, https://doi.org/10.1186/s12969-019-0365-y.

[30] C.L. Mcatee, J. Lubega, K. Underbrink, K. Curry, P. Msaouel, M. Barrow, et al., Association of rituximab use with adverse events in children, adolescents, and young adults, JAMA Netw. Open 4 (2) (2021) e2036321, https://doi.org/10.1001/jamanetworkopen.2020.36321.