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Original article

SERUM IMMUNOGLOBULIN LEVEL FOLLOWING THE TREATMENT IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, requiring intensive chemotherapy that can lead to immune suppression and secondary immunodeficiency. This study evaluates serum immunoglobulin (Ig) levels before and after intensive therapy in children with ALL.

Methods: Serum levels of IgA, IgG, and IgM were analyzed in children with ALL before chemotherapy initiation and after completing intensive treatment. Results were compared with a healthy control group. Statistical analysis was performed using the t-test, with significance set at $p < 0.05$.

Results: Before treatment, Ig levels in children with ALL did not differ significantly from those in the healthy control group ($p > 0.05$). However, after intensive therapy, IgA, IgG, and IgM levels showed a significant decline ($p < 0.05$). The decrease was more pronounced in children aged 6 to 12 years.

Conclusion: Intensive chemotherapy leads to a significant reduction in serum immunoglobulin levels, increasing the risk of infections. The results highlight the need for further research on intravenous immunoglobulin (IVIG) supplementation as a potential strategy to improve immune function in pediatric ALL patients undergoing treatment.

Keywords: acute lymphoblastic leukemia, secondary immunodeficiency, immunoglobulin therapy

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disease of lymphoid cells that occurs due to the stop of differentiation and proliferation of early lymphoid precursors which replace normal hematopoietic cells in the bone marrow[1]. Leukemia is the leading malignant disease in children aged 0-14, followed by CNS tumors and lymphomas[2,3]. The peak incidence of ALL occurs between the ages of 1 and 5 years [1]. In North Macedonia, acute leukemia is the most frequently diagnosed childhood malignancy, accounting for approximately 35% of cases.

The treatment of ALL follows a standardized protocol consisting of four phases over two years: induction, consolidation, reinduction, and maintenance therapy [4-8].

For high-risk patients with therapy-resistant disease or relapse, allogeneic hematopoietic stem cell transplantation is a viable therapeutic option. Additionally, novel treatment approaches, including targeted therapy with monoclonal antibodies and CAR-T cell therapy, are being increasingly utilized.

Advancements in diagnosis and treatment over the past few decades have significantly improved therapeutic outcomes. Over the last 40 years, complete remission has been achieved in more than 90% of children with acute lymphoblastic leukemia. As survival rates increase, there is a growing emphasis on long-term follow-up to monitor early and late complications associated with antineoplastic treatment[1,3,9].

One of the most common complications in malignant diseases and chemotherapy is immune system suppression, leading to secondary immunodeficiency. This condition arises from both the malignancy itself and the cytotoxic effects of chemotherapy [10-16]. Secondary immunodeficiency (SID) is clinically characterized by increased susceptibility to infections, including opportunistic and atypical infections. In many cases, SID-related immune system impairment is reversible [16,17]. Infections remain a major cause of morbidity and mortality in these patients. Infections prolong the entire treatment process and often pose a serious life-threatening risk[10,18-21].

There has been increasing interest in assessing immune status in children with malignancies during and after chemotherapy [20,22,23]. Research has also explored the potential role of adjunctive therapies, such as intravenous immunoglobulin (IVIG) supplementation, in mitigating the effects of SID and improving treatment outcomes [21,24]. Several strategies for optimizing IVIG therapy—including initiation timing, dosing, and discontinuation—have been investigated [25]. A consensus among 32 European experts in SID, immunology, and pediatric hemato-oncology has established clear guidelines for IVIG administration in patients with hematologic malignancies undergoing chemotherapy [24].

This study aims to evaluate serum immunoglobulin levels in children with ALL before the initiation of chemotherapy and after the completion of intensive therapy (following Protocol I).

Materials and methods

This is an analytical retrospective study, carried out at the Department of Hemato-oncology and Immunology of the University Clinic for Children's Diseases in Skopje. The data (personal data - gender, age, and blood immunoglobulin values) were taken from the medical history of patients and the electronic database system (HIS-system - Hospital information system). The results of 20 patients with acute lymphoblastic leukemia aged 2-12 years, diagnosed in 2019 and 2020, were analyzed. Among the studied group, 12 patients were male, and 8 were female. The average age of the studied group was 4.37 years (Table 1). Levels of serum immunoglobulins (IgA, IgG, IgM) in children both before starting therapy and after intensive therapy were analyzed. All children were treated according to the BFM (ALL-IC 2002) protocol.

Inclusion criteria: Children aged 2-12 years at the beginning of diagnosed acute lymphoblastic leukemia (T-cell or B-cell ALL), and at the end of intensive therapy according to the BFM (ALL-IC 2002) protocol.

Exclusion criteria: Children under 2 years of age, children with primary immunodeficiency, and children with ALL as part of a genetic disease.

The results of the study group were compared with a control group of healthy children. The control group consisted of 20 healthy outpatient children aged 2-12 years, 11 females, and 9 males (mean age 4.9 years) who came as outpatients in the clinic, asking for advice for their further immunization (Table 1).

Table 1. Number and age of children diagnosed with acute lymphoblastic leukemia (study group - SG) and healthy children (control group - CG)

	Study group (SG) N (%)	Control group N (%)
Sex		
Male	12(60)	9(45)
Female	8(40)	11(55)
Age (years)		
2-6	15(75)	13(65)
6-12	5(25)	7(35)

The levels of immunoglobulins in the blood (IgA, IgG, and IgM) were measured using the turbidimetric method on the Architect c4000 biochemical analyzer in the Laboratory of the University Clinic for Children's Diseases, Skopje.

The data were compiled and analyzed using IBM SPSS Statistics 20.0 (IBM, Somers, NY). Measures of central tendency (mean) and dispersion (standard deviation) were calculated. The Student's t-test was used to compare differences between two arithmetic means. The rate of change over time (from the start to the end of therapy) was assessed using the index of dynamics.

Results

Serum Ig levels in the study group (SG) were analyzed before initiation of chemotherapy and after the completion of intensive care.

The average IgA level before chemotherapy was 0.8±0.5 and at the end of therapy 0.6±0.3. Analysis of the results, according to the t-test, showed a statistically significant difference between the two test points ($p<0.05$) (Table 2, Figure 1).

Table 2. Average level of IgA, IgG, and IgM before initiation of therapy and at the end in SG

Serum level of Ig	Before therapy(g/l)	End of therapy(g/l)	p
IgA	0.84+/-0.47	0.56+/-0.26	0.02 *
IgG	9.48+/-2.86	5.90+/-2.32	0.00002 *
IgM	1.00+/-0.61	0.32+/-0.11	0.00005 *

t-test

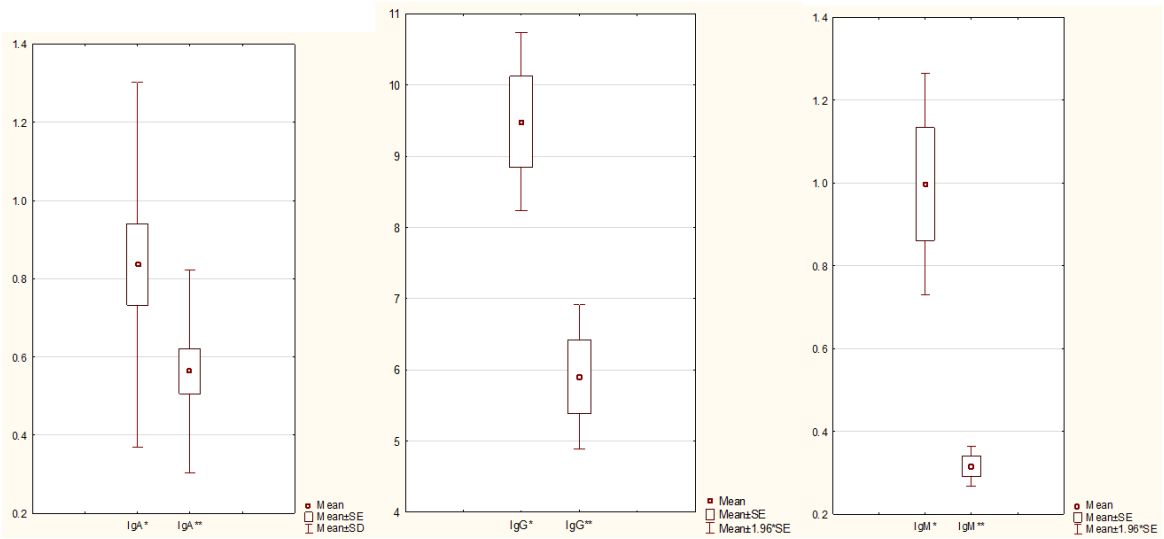

Fig. 1. Display of the average level of IgA, IgG, and IgM before initiation of therapy and at the end in SG

The mean IgG before chemotherapy was 9.5±2.9 and at the end of therapy 5.9±2.3. The analysis of the results, according to the t-test, was statistically significant for $p<0.05$ (Table 2 and Figure 1).

The mean IgM level before chemotherapy was 1.0±0.6 and at the end of therapy 0.3±0.1. According to the t-test, the difference was statistically significant for $p<0.05$ (Table 2 and Figure 1).

Table 3 shows serum immunoglobulin levels before chemotherapy initiation in the study group compared to immunoglobulin levels in the healthy control group of children.

The mean IgA before chemotherapy was 0.8±0.5 in the study group and 0.9±0.5. in the control group. According to the t-test, the difference was statistically not significant for $p> 0.05$. The mean IgG before chemotherapy was 9.5±2.9 in the study group, and 8.4±2.4 in the control group. According to the t-test, the difference was statistically insignificant for $p> 0.05$. The mean IgM before chemotherapy was 1.0±0.6 in the study group, and 1.3±1.3 in the healthy control group. According to the t-test, the difference was statistically insignificant for $p> 0.05$. (Table 3 and Figure 2).

These findings suggest that serum immunoglobulin levels before the initiation of chemotherapy in children with acute leukemia do not significantly differ from those in the healthy control group.

Table 3. Average level of IgA, IgG, and IgM before initiation of therapy in SG and CG

Serum level of Ig	SG Before therapy (g/l)	CG (g/l)	p
IgA	0.8+/-0.47	0.9+/-0.48	0.496
IgG	9.5+/-2.86	8.4+/-2.42	0.221
IgM	1.0+/-0.61	1.3+/-1.35	0.402

t-test

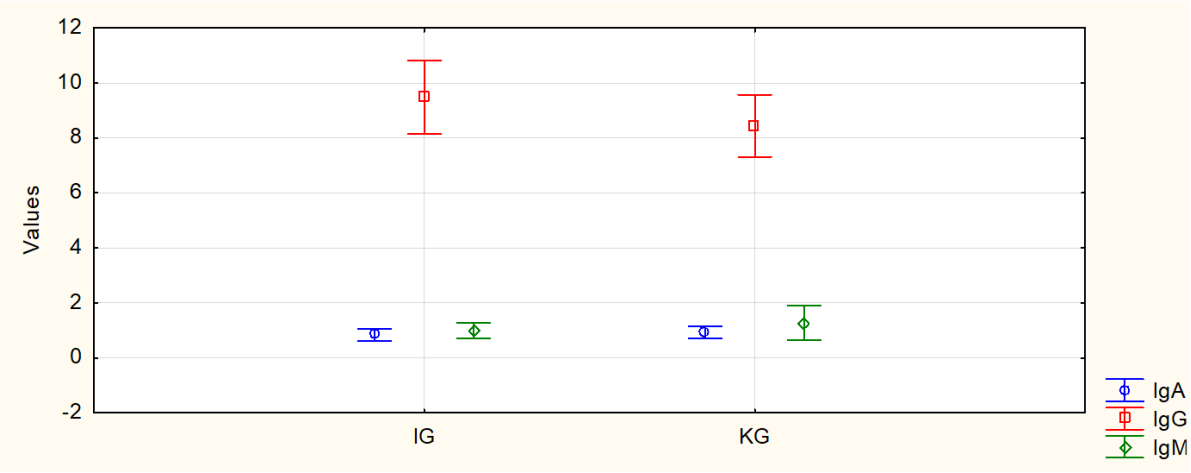

Fig. 2. Presentation of average value of IgA, IgG, IgM before initiation of therapy in SG and CG

According to the dynamic indices of IgA, IgG, and IgM, there was a larger downward trend in serum immunoglobulin levels in patients aged 6 to 12 years (Table 4).

Table 4. A downward trend in serum immunoglobulin levels in SG after completion of intensive care by age

	IgA	IgG	IgM
Dynamics Index (2-6 years)	28.6%	36.8%	62.5%
Dynamics Index (6-12 years)	50%	39.3%	81.25%

Discussion

The findings of our study demonstrate that children with acute lymphoblastic leukemia (ALL) experience a significant reduction in serum immunoglobulin (Ig) levels following the completion of intensive therapy. Statistical analysis confirms a significant difference ($p < 0.05$) in Ig levels before and after treatment. However, no statistically significant difference ($p > 0.05$) was observed between pre-treatment Ig levels in ALL patients and those in the healthy control group. Our data suggest that the decline in IgA, IgG, and IgM levels is more pronounced in children aged 6 to 12 years.

The interest in analyzing the immune status of children with malignant disease during and after the completion of chemotherapy has been the subject of increasing research in recent years[20,22,23].

Our results align with the findings of Martin Ibanez *et al.* All children with ALL at the time of diagnosis of the disease had normal immunoglobulin concentration. During treatment, the majority of patients had immunoglobulin deficiency, being IgG and IgM the most affected immunoglobulins[26].

Ince *et al.* also found that children who had been fully vaccinated were at great risk of infection due to the decrease in protective antibody levels after chemotherapy[27].

Given the increasing interest in assessing immune status during and after chemotherapy, further research is warranted. Recent studies have explored the potential role of intravenous immunoglobulin (IVIG) supplementation as an adjunctive therapy to mitigate immune suppression in pediatric oncology patients [21,24]. The EMA (European Medicines Agency) approved the expanded use of immunoglobulin intravenous substitution therapy (IgRT) for SID in 2021[28]. Clinical studies indicate that IVIG therapy reduces infection rates and enhances quality of life in immunocompromised patients [25,29-32].

Conclusion

One of the most common complications of ALL and chemotherapy is the suppression of the humoral immune system. Children diagnosed with ALL had normal IgA, IgG, and IgM concentrations at the time of diagnosis, but after completing intensive treatment with ALL-IC 2002 protocol, the majority of patients showed a decrease in the concentration of immunoglobulin. Ig levels showed a greater rate of decline in patients aged 6-12 years. Our preliminary results highlight the necessity for more in-depth investigations to evaluate the potential integration of Ig therapy into intensive chemotherapy protocols. Further research will help establish guidelines for immunoglobulin replacement in pediatric patients undergoing treatment for ALL

Conflict of interest statement. None declared.

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