Prevalence and Safety of Intravenous Immunoglobulin Administration During Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukemia in First Complete Remission: A Health Maintenance Organization Perspective

Patrick Van Winkle, MD; Raoul Burchette, MA, MS; Raymond Kim, CCRP; Rukmani Raghunathan, MD; Naveen Qureshi, MD

Perm J 2018;22:17-141

E-pub:04/09/2018

https://doi.org/10.7812/TPP/17-141

ABSTRACT

Context: Children with acute lymphoblastic leukemia (ALL) in first complete remission (CR1) experience hypogammaglobulinemia and are at risk of sepsis during maintenance chemotherapy. Intravenous immunoglobulin (IVIG) has been used to try to circumvent this risk, but no data exist regarding its safety and prevalence in a health maintenance organization.

Objective: To evaluate the prevalence and safety of IVIG in children with ALL in CR1 during maintenance chemotherapy.

Design: A multicenter, retrospective cohort study of consecutive children with ALL in CR1 during maintenance chemotherapy from 2008 to 2014. Groups treated with or without IVIG were compared using nonparametric statistics. Multivariate logistic regression involved all variables available before maintenance therapy began.

Results: One hundred eighteen patients were included (53% males), aged 9 months to 19 years. Thirty of 31 patients (97%) who had immunoglobulins analyzed before IVIG were hypogammaglobulinemic. Thirty-six patients (30%) received IVIG during maintenance chemotherapy. Patients received an average of 10.5 IVIG doses (range = 1-31). Ninety-seven percent of doses were administered without a transfusion reaction. Other factors associated with IVIG use were prior double-delayed intensification (odds ratio = 5.36, 95% confidence interval = 1.3-27.49, p = 0.026) and episodes of bacteremia or fungemia before maintenance chemotherapy (odds ratio = 3.04, 95% confidence interval = 1.25-7.51, p = 0.015).

Conclusion: Use of IVIG in children with ALL in CR1 with hypogammaglobulinemia occurred in approximately 30% of patients and was well tolerated. Administration of IVIG significantly correlated with a history of double-delayed intensification and prior bacteremia or fungemia.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common type of cancer seen in children.[1] Immunosuppression, secondary to the underlying disease process as well as treatment with chemotherapy, puts these patients at risk of infectious complications, with patients receiving high-risk protocols more at risk than those on standard-risk protocols.[2,3] These infectious complications often lead to hospitalization and can be clinically significant, such as with bacteremia or fungemia.[4,5]

Past studies have shown a marked immunosuppression, particularly a significant reduction in B lymphocytes,[6-13] and associated hypogammaglobulinemia, during the maintenance phase of chemotherapy for childhood ALL. Intravenous immunoglobulin (IVIG) has been used in a variety of clinical settings to reduce the frequency and severity of bacterial infections in pediatric and adult patients with primary and secondary antibody deficiencies.[14] Treatment with IVIG has been variably shown to decrease the risk of infection in specific disease processes associated with hypogammaglobulinemia, such as after transplant in bone marrow transplant recipients, in whom it has overall not been shown to decrease the risk of infection or all-cause mortality,[15] and in chronic lymphoid leukemia and multiple myeloma, for which it has been shown to decrease infection but not mortality.[16]

In the context of childhood ALL, past studies evaluated the use of IVIG before maintenance chemotherapy. Gimesi et al[17] conducted a prospective, randomized study of 60 children with ALL: 30 in the IVIG group and 30 receiving the same chemotherapy without IVIG. They demonstrated a decrease in the number of identified infections and a decrease in the number and duration of antibiotic treatments with the use of IVIG in the first 6 months of treatment before the start of maintenance chemotherapy.[17] Additionally, IVIG has been used to augment antibiotic treatment in children with leukemia and fever and neutropenia. Sumer et al[18] randomly assigned 33 children to receive either antibiotics with IVIG or antibiotics without IVIG. They found that the duration of fever in the IVIG group was significantly shorter, although the duration of interruption of chemotherapy and length of hospitalization and neutropenia were not different. These studies did show some benefit but were completed at a time that does not reflect current chemotherapy intensities. They also did not evaluate the use of IVIG in the setting of prophylaxis in maintenance chemotherapy. Thus,

Patrick Van Winkle, MD, is a Pediatric Hospitalist at the Anaheim Medical Center in CA. E-mail: patrick.j.vanwinkle@kp.org. **Raoul Burchette, MA, MS,** is a Statistician for Kaiser Permanente Southern California Research and Evaluation in Pasadena. E-mail: raoul.j.burchette@kp.org. **Raymond Kim, CCRP,** is a Research Assistant for Kaiser Permanente Southern California Research and Evaluation in Pasadena. E-mail: rwhkim@gmail.com. **Rukmani Raghunathan, MD,** is a Pediatric Oncologist in the Department of Pediatric Hematology and Oncology at the Anaheim Medical Center in CA. E-mail: rukmani.raghunathan@kp.org. **Naveen Qureshi, MD,** is a Pediatric Oncologist in the Department of Pediatric Hematology and Oncology at the Anaheim Medical Center in CA. E-mail: naveen.a.qureshi@kp.org.

although IVIG has been evaluated in other settings, its use has not been evaluated in the context of maintenance chemotherapy in pediatric ALL.

IVIG is an intensive treatment both in terms of the risk and involvement for the patient and from a cost and utilization standpoint for health care providers. Currently, there is no consensus on the use of IVIG in hematologic malignancies in general[19] and specifically in children with ALL and treatment-associated hypogammaglobulinemia. The Supportive Care Guidelines from the Children's Oncology Group recommend, "If clinically indicated, IgG [immunoglobulin G] levels may be monitored throughout treatment. If the IgG level falls below age-determined normal levels, IVIG at 400 mg/kg may be administered at the discretion of the investigator."[20]

The aim of our current study is to determine the prevalence and safety of IVIG during maintenance chemotherapy in children with ALL in first complete remission, including the indications for its initiation and discontinuation. We compared the IVIG and non-IVIG groups in terms of risk stratification at diagnosis and infectious complications both before and during maintenance chemotherapy.

METHODS

This study is a multicenter retrospective cohort of patients with ALL aged 9 months to 19 years cared for in our health maintenance organization (HMO) from January 1, 2008, to July 1, 2014. Our HMO currently cares for approximately 900,000 children younger than age 18 years. We have 5 Medical Centers located in 4 counties that care for pediatric cancer patients; all 5 Medical Centers have Pediatric Inpatient Units, and 3 have Pediatric Intensive Care Units, one of which is our primary tertiary care center. Our integrated medical group has regional oversight and a single electronic medical record, but each Medical Center has local control over clinical practice. There are no standard operating procedures for measuring immunoglobulin G (IgG) levels or administering IVIG outside of clinical trial requirements. The dosing of IVIG is standard, however, in our group, at 400 mg/kg per dose.

Patient Selection

Patients with ALL were selected for the study on the basis of International Classification of Diseases, Ninth Revision (ICD-9) codes 204xx and 208xx. This list was cross-referenced with data available from the Children's Oncology Group registry that captures patients enrolled in a study protocol. Patients were excluded from the study for the following reasons: Younger than 6 months of age at time of diagnosis, relapse of ALL or receipt of bone marrow transplant, concurrent or prior additional malignancies, and Down syndrome. Patients also had to have completed at least 12 months of maintenance chemotherapy to be included in the study. Patients with relapse were included if they completed at least 12 months of maintenance chemotherapy before relapse, and only the data before relapse were considered.

Once the patients were identified by ICD-9 codes, the electronic medical record, which contains both inpatient and outpatient data, was reviewed and data were recorded on a standardized information sheet. Each chart was reviewed by both the research assistant and the principal investigator. Treatment roadmaps, stored in the outpatient oncology clinics, were also used to augment and verify information.

In this article, the five Medical Centers caring for our pediatric patients are given the title Medical Center (MC)-A through E; the specific geographic locations of the centers are blinded for

Table 1. Demographic and treatment characteristics of patients who received or did not receive IVIG[a]

Characteristic	IVIG group (N = 36), no. (%)	Non-IVIG group (N = 82), no. (%)	p value
Mean age at diagnosis, years (range)	7.9 (0.8-19.8)	7.1 (1.5-18.7)	0.401
Sex			0.476
Female	15 (42)	40 (49)	
Male	21 (58)	42 (51)	
Race/ethnicity			0.718
African American	1 (3)	5 (6)	
Asian	3 (8)	5 (6)	
White	7 (19)	22 (27)	
Hispanic	24 (67)	47 (57)	
Pacific Islander	1 (3)	1 (1)	
Unknown	0 (0)	2 (2)	
Medical Center (MC)			0.002
MC-A	11 (31)	5 (6)	
MC-B	2 (6)	10 (12)	
MC-C	12 (33)	32 (39)	
MC-D	7 (19)	10 (12)	
MC-E	4 (11)	25 (30)	
Treatment protocol[b]			0.244
AALL0232	17 (47)	22 (27)	
AALL0331	13 (36)	36 (44)	
AALL0434	3 (8)	9 (11)	
AALL0932	3 (8)	14 (17)	
AALL1131	0 (0)	1 (1)	
High risk at diagnosis			0.055
No	16 (44)	52 (63)	
Yes	20 (56)	30 (37)	
Central nervous system disease at presentation			0.546
No	35 (97)	81 (99)	
Yes	1 (3)	1 (1)	
Received cranial irradiation			0.652
No	31 (86)	73 (89)	
Yes	5 (14)	9 (11)	
Received double-delayed intensification			0.005
No	29 (81)	79 (96)	
Yes	7 (19)	3 (4)	
Received high-dose methotrexate			0.428
No	24 (67)	62 (76)	
Yes	12 (33)	20 (24)	

[a] Some percentages do not total to 100 because of rounding.
[b] The Children's Oncology Group studies for the treatment of acute lymphoblastic leukemia (AALL0232, AALL0331, AALL0434, AALL0932, AALL1131).
IVIG = intravenous immunoglobulin.

this analysis. Indications for initiation and discontinuation of IVIG were obtained from physician notes.

This study was approved by the Kaiser Permanente Southern California institutional review board according to the Declaration of Helsinki and federal regulations.

Statistical Analysis

Descriptive statistics were computed for all the variables by group (IVIG vs non-IVIG). Comparisons between the groups used nonparametric statistics, including χ^2, Wilcoxon rank sum, and signed rank tests as appropriate. Univariate logistic regression examinations of each variable with the outcome of interest; IVIG given (group membership) were also computed.

The multivariate analysis involved all variables from the univariate analysis with p values less than 0.25 that were available before the beginning of maintenance chemotherapy. We examined the interrelationship between these variables with a cross-correlation table and verified that there was a real basis for the relationships revealed. These variables were then put together into a logistic regression model and various variable-selection (backward and forward stepwise, scoring) algorithms were used to see if adequate explanations of the prescribing pattern for IVIG could be determined from the variously selected variables. Variables that correlated too highly with the other variables were removed from the model because of potential multicollinearity problems.

RESULTS

One hundred eighteen patients were included in the analysis, 63 (53%) of whom were male, with an age range from 9 months to 19 years. Table 1 represents the demographic and treatment characteristics of the IVIG group and non-IVIG group.

Thirty-six patients (30%) received IVIG during maintenance chemotherapy for the following reasons (as stated in the physicians' notes): Infection before start of maintenance chemotherapy (n = 5), infection during maintenance chemotherapy (n = 16), prophylaxis for viral exposure during maintenance chemotherapy (n = 4), and decreased immunoglobulin levels only in an otherwise clinically stable patient (n = 11). The infections before maintenance chemotherapy included 2 patients with bacteremia, 2 with fungemia, and 1 with viremia. The infections during maintenance chemotherapy included 6 patients with bacteremia, 5 with viremia, and 5 with fever and neutropenia. In the prophylaxis group, 3 patients were exposed to herpes virus and 1 to rubella.

For the IVIG group (N = 36), IgG levels were checked 243 times, with an average of 7 (range = 2-33) levels per patient. The mean IgG level for 31 of the 36 IVIG patients who had levels checked before administration of IVIG was 474 mg/dL (standard error of the mean = 33.7 mg/dL), and the range was from 89 mg/dL to 785 mg/dL. (The lower limit of normal, as reported by the laboratory, for IgG ranged from 501 mg/dL to 757 mg/dL at various times that the levels were sent.) For IgG, 24 of the 31 patients had levels below the lower limit for normal at the time IVIG therapy was initiated.

The reasons for discontinuation of IVIG treatment, as stated in the physicians' notes, were as follows: End of chemotherapy (n = 16), immunoglobulin levels returned to normal range (n = 7), single dose given for infection (n = 2) or prophylaxis for viral exposure (n = 4), ongoing at the end of the study period (n = 3), parental refusal of additional doses (n = 2), and patient's leukemia relapsed and thus the patient was removed from analysis (n = 2). Of the 36 patients who received IVIG, only 7 had levels checked within 1 month after the time of discontinuation.

A total of 376 doses of IVIG were given to the 36 patients, with an average of 10.5 (range = 1-31) doses per patient. For nearly all patients who were given more than 1 dose of IVIG, the doses were given at consecutive 1-month intervals. Three hundred sixteen doses were given in the clinic, and 53 doses were given in the inpatient setting. For the remaining 7 doses, there was insufficient documentation to determine where they were given.

We reviewed the nursing notes for the 316 doses given in the clinic for adverse reactions, as based on the Common Terminology Criteria for Adverse Events.[21] We found that for 306 doses (96.8%) there was no adverse reaction noted, 1 patient had a Grade 1 reaction, 8 patients had Grade 2 reactions, and 1 patient had a Grade 3 reaction. There were no Grade 4 or 5 reactions. For the Grade 2 reactions, infusions were temporarily interrupted for the following reasons: Low-grade fever that resolved (n = 3), nausea and vomiting (n = 2), headache (n = 2), and chills (n = 1). The Grade 3 reaction was a fever in a neutropenic patient who was subsequently admitted.

Comparison between Medical Centers

There was a statistically significant difference in the mean number of IVIG doses given between Medical Centers (p = 0.008): MC-A, 15.5 (range = 4-29); MC-B, 12.5 (range = 6-19); MC-C, 12.3 (range = 1-31); MC-D, 3.4 (range = 1-8); and MC-E, 2.8 (range = 1-8). There was also a statistically significant difference between Medical Centers in the number of times that immunoglobulin levels were checked (n = 118; p < 0.001): MC-A, 4.7 (range = 0-10); MC-B, 1.4 (range = 0-7); MC-C, 1.3 (range = 0-7); MC-D, 13 (range = 1-33); and MC-E, 1.2 (range = 0-6).

Comparison of IVIG and non-IVIG Groups

The univariate analysis of infectious complications before maintenance chemotherapy for IVIG vs non-IVIG groups is shown in Table 2. Patients receiving IVIG had significantly more days between treatment initiation and maintenance initiation vs

Table 2. Infectious complications before maintenance chemotherapy for IVIG and non-IVIG groups

Complication factors	IVIG group (N = 36), mean (SEM)	Non-IVIG group (N = 82), mean (SEM)	p value[a]
Days of treatment from induction to maintenance chemotherapy	279 (11.0)	244 (6.7)	0.004
Episodes of bacteremia or fungemia	0.89 (0.2)	0.26 (0.1)	0.002
Hospitalizations	2.3 (0.4)	1.9 (0.2)	0.465
Days of hospitalization	20.4 (4.3)	11.5 (1.3)	0.264

[a] p values take into account days of therapy.
IVIG = intravenous immunoglobulin; SEM = standard error of the mean.

the non-IVIG group (p = 0.004) and a history of significantly more episodes of bacteremia or fungemia (p = 0.002). During maintenance chemotherapy, there were no significant differences in infectious complications or days of treatment for IVIG vs non-IVIG groups (Table 3). Table 4 shows the multivariate analysis of factors associated with IVIG use. Most importantly, patients receiving double-delayed intensification chemotherapy and those with a history of either a bacteremia or fungemia had a significantly higher chance of receiving IVIG (odds ratio = 5.36, 95% confidence interval = 1.3-27.49, p = 0.026; and odds ratio = 3.04, 95% confidence interval = 1.25-7.51, p = 0.015, for bacteremia and fungemia, respectively).

Table 3. Infectious complications during maintenance chemotherapy for IVIG and non-IVIG groups

Complication factors	IVIG group (N = 36), mean (SEM)	Non-IVIG group (N = 82), mean (SEM)	p value[a]
Days of maintenance chemotherapy	713 (33.2)	736 (22.8)	0.617
Episodes of bacteremia	0.25 (0.09)	0.15 (0.04)	0.336
Hospitalizations	1.9 (0.3)	1.7 (0.2)	0.302
Days of hospitalization	11.1 (2.3)	6.7 (0.9)	0.112
Number of infections treated with antibiotics on an outpatient basis	4.8 (0.8)	4.7 (0.4)	0.756

[a] p values take into account days of therapy.
IVIG = intravenous immunoglobulin; SEM = standard error of the mean.

Table 4. Multivariate analysis of variables before maintenance chemotherapy associated with IVIG use[a]

Variable	Odds ratio	95% confidence interval	p value[b]
Did not receive double-delayed intensification	1		
Received double-delayed intensification chemotherapy	5.36	1.3-27.49	0.026
Did not have episode of bacteremia or fungemia before maintenance chemotherapy	1		
Had episode of bacteremia and fungemia before maintenance chemotherapy	3.04	1.25-7.51	0.015
Average risk at diagnosis	1		
High risk at diagnosis	1.7	0.72-4.01	0.22

[a] Length of treatment was removed from analysis because of interrelatedness with other variables.
[b] In univariate analysis, p < 0.25.
IVIG = intravenous immunoglobulin.

DISCUSSION

Thirty percent of our patients received IVIG during maintenance chemotherapy, most of whom had hypogammaglobulinemia before IVIG initiation. The multivariate analysis showed a significant relationship between the use of IVIG and patients who received double-delayed intensification and/or had bacteremia or fungemia before maintenance chemotherapy. Past studies have shown that patients are at higher risk of infection during maintenance chemotherapy if they received more intensive regimens before maintenance. A study by van Tilburg et al[3] evaluated infectious complications in patients with ALL in standard-risk and medium-risk categories in the initial 2 years of treatment and found an increase in hospitalizations because of fever in the first half of the intensification/maintenance phase (20-62 weeks after diagnosis). These researchers also showed a significant increase in hospital admissions, days of hospitalization, and episodes of bacteremia in the higher-risk group.[3] Kaul et al[2] performed a treatment-related cost analysis of hospitalizations in the first year of treatment for ALL and found a significantly increased rate of admissions and hospital days for admission in high-risk compared with standard-risk patients. We add to this literature by showing a specific association between the higher-dose chemotherapy and infectious complications before maintenance chemotherapy with the use of IVIG during maintenance chemotherapy.

We furthermore demonstrate that the administration of IVIG in this clinical setting is safe, with no significant reactions in 96.8% of all infusions, minor reactions in 8 other patients, and only 1 neutropenic patient who had to be admitted to the hospital because of fever that started during the IVIG infusion. There were no incidents of serious allergic reaction or anaphylaxis, and no patients required corticosteroids or epinephrine.

Four of the patients in our study were given IVIG as prophylaxis for viral exposure. None of the four children had symptoms of the viral illness after administration of IVIG. A study by van Tilburg et al[22] showed a decrease in antibody levels against vaccine-preventable diseases in children with ALL. In a small study of five children with leukemia who were exposed to varicella and then given IVIG, clinical infection did not develop in any of the children.[23] Our study adds an additional limited piece of evidence to this practice.

The patients in this study were treated at one of five HMO Medical Centers that are located across Southern California. Ours is an integrated system in terms of physician partnership, hospital system, and an integrated computer system, but there is local control over clinical practice. In this study we found a significant variation in clinical practice between Medical Centers around the use of IVIG. There was a significant difference in the percentage of patients who received IVIG, the number of doses received, and the number of immunoglobulin levels that were checked. There was also variation in the stated indications for the use of IVIG, the length of IVIG use, and indications for discontinuation. This variation in practice is not surprising in the context of the paucity of literature available on the use of IVIG in this setting. Because IVIG is costly in terms of involvement and risk of severe infusion-related reactions to the patient as well as from a utilization standpoint for the health care system, having a more evidence-based, uniform practice would be beneficial.

There are limitations to our study. Because this was a retrospective study, we were not able to obtain certain types of data, such as specific infections treated on an outpatient basis.

Documentation for certain data points, such as outpatient antibiotic prescriptions, might not have been complete in a small subset of patients. Last, not all the patients in the sample completed the full course of maintenance chemotherapy before the end of the study period.

CONCLUSION

In a large HMO cohort of children with ALL in first complete remission who received IVIG, nearly all were hypogammaglobulinemic at the time of administration in the maintenance phase, and the IVIG infusions were well tolerated. Most importantly, the prevalence of IVIG administration in this population was significantly correlated with a history of administration of double-delayed intensification and/or prior bacteremia or fungemia. Future prospective studies are indicated to determine clinical utility and to standardize the parameters for the use of IVIG in maintenance chemotherapy in children with ALL in first complete remission. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

This research was supported by a grant from the Regional Research Committee of Kaiser Permanente Southern California.

This work was presented at the American Society of Pediatric Hematology/Oncology Annual Meeting, May 7, 2015, in Phoenix, AZ, and at the Kaiser Permanente Southern California Oncology Symposium on June 11, 2015, in Long Beach, CA.

The authors wish to thank Erin Morris, RN, Maria Fareri Children's Hospital, Valhalla, NY, for her assistance in formatting and preparing the manuscript for publication. We also thank Mitchell S Cairo, MD, Professor of Pediatrics, Medicine, Pathology, Microbiology and Immunology and Cell Biology and Anatomy, Maria Fareri Children's Hospital, for his contribution in the review of this manuscript.

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

How to Cite this Article

Van Winkle P, Burchette R, Kim R, Raghunathan R, Qureshi N. Prevalence and safety of intravenous immunoglobulin administration during maintenance chemotherapy in children with acute lymphoblastic leukemia in first complete remission: A health maintenance organization perspective. Perm J 2018;22:17-141. DOI: https://doi.org/10.7812/TPP/17-141

References

1. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975-2013 [Internet]. Bethesda, MD: National Cancer Institute; 2016 Apr [updated 2016 Sep 12; cited 2017 Dec 20]. Available from: https://seer.cancer.gov/archive/csr/1975_2013/.
2. Kaul S, Korgenski EK, Ying J, et al. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. Cancer Med 2016 Feb;5(2):221-9. DOI: https://doi.org/10.1002/cam4.583.
3. van Tilburg CM, Sanders EA, Nibbelke EE, et al. Impact of reduced chemotherapy treatment for good risk childhood acute lymphoblastic leukaemia on infectious morbidity. Br J Haematol 2011 Feb;152(4):433-40. DOI: https://doi.org/10.1111/j.1365-2141.2010.08463.x.
4. Lex C, Körholz D, Kohlmüller B, et al. Infectious complications in children with acute lymphoblastic leukemia and T-cell lymphoma—a rationale for tailored supportive care. Support Care Cancer 2001 Oct;9(7):514-21. DOI: https://doi.org/10.1007/s005200100248.
5. Rahiala J, Perkkiö M, Riikonen P. Infections occurring during the courses of anticancer chemotherapy in children with ALL: A retrospective analysis of 59 patients. Pediatr Hematol Oncol 1998 Mar-Apr;15(2):165-74. DOI: https://doi.org/10.3109/08880019809167231.
6. Caver TE, Slobod KS, Flynn PM, et al. Profound abnormality of the B/T lymphocyte ratio during chemotherapy for pediatric acute lymphoblastic leukemia. Leukemia 1998 Apr;12(4):619-22. DOI: https://doi.org/10.1038/sj.leu.2400970.
7. de Vaan GA, van Munster PJ, Bakkeren JA. Recovery of immune function after cessation of maintenance therapy in acute lymphoblastic leukemia (ALL) of childhood. Eur J Pediatr 1982 Oct;139(2):113-7. DOI: https://doi.org/10.1007/bf00441492.
8. El-Chennawi FA, Al-Tonbary YA, Mossad YM, Ahmed MA. Immune reconstitution during maintenance therapy in children with acute lymphoblastic leukemia, relation to co-existing infection. Hematology 2008 Aug;13(4):203-9. DOI: https://doi.org/10.1179/102453308X316086.
9. 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 Nov;147(3):360-70. DOI: https://doi.org/ 10.1111/j.1365-2141.2009.07862.x.
10. Martín Ibáñez I, Arce Casas A, Cruz Martínez O, Estella Aguado J, Martín Mateos MA. Humoral immunity in pediatric patients with acute lymphoblastic leukaemia. Allergol Immunopathol (Madr) 2003 Nov-Dec;31(6):303-10. DOI: https://doi.org/10.1016/s0301-0546(03)79203-9.
11. Kostaridou S, Polychronopoulou S, Psarra K, et al. Decrease of CD4+ and B-lymphocyte populations is not associated with severe infectious complications in children with acute lymphoblastic leukemia during maintenance. Int J Hematol 2004 Nov;80(4):354-60. DOI: https://doi.org/10.1532/ijh97.e0317.
12. Luczynski W, Stasiak-Barmuta A, Krawczuk-Rybak M. Immunologic monitoring of maintenance therapy for acute lymphoblastic leukaemia in children—preliminary report. Pediatr Blood Cancer 2004 May;42(5):416-20. DOI: https://doi.org/10.1002/pbc.20018.
13. Wakiguchi H, Fujieda M, Hisakawa H, Kubota H, Matsumoto K, Kurashige T. IgG subclass imbalance in children with acute lymphoblastic leukemia receiving maintenance chemotherapy. Acta Paediatr Jpn 1992 Jun;34(3):278-81. DOI: https://doi.org/10.1111/j.1442-200x.1992.tb00959.x.
14. Mouthon L, Lortholary O. Intravenous immunoglobulins in infectious diseases: Where do we stand? Clin Microbiol Infect 2003 May;9(5):333-8. DOI: https://doi.org/10.1046/j.1469-0691.2003.00694.x.
15. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: Systematic review and meta-analysis. J Clin Oncol 2009 Feb;27(5):770-81. DOI: https://doi.org/10.1200/jco.2008.16.8450.
16. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: Systematic review and meta-analysis. Leukemia & Lymphoma 2009 May;50(5):764-72. DOI: https://doi.org/10.1080/10428190902856824.
17. Gimesi A, Eibl M, Koós R, et al. Immunoglobulin prophylaxis during intensive treatment of acute lymphoblastic leukemia in children. Acta Paediatr Hung 1992;32(2):115-25.
18. Sumer T, Abumelha A, al-Mulhim I, al-Fadil M. Treatment of fever and neutropenia with antibiotics versus antibiotics plus intravenous gammaglobulin in childhood leukemia. Eur J Pediatr 1989 Feb;148(5):401-2. DOI: https://doi.org/10.1007/bf00595896.
19. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Cochrane Database Syst Rev 2008 Oct 8;(4):CD006501. DOI: https://doi.org/10.1002/14651858.CD006501.pub2.
20. COG supportive care guidelines AALL0232 [Internet]. Monrovia, CA: The Children's Oncology Group; 2013 March 25 [cited 2017 Dec 20]. Available from: https://cogmembers.org/Prot/AALL0232/AALL0232DOC.pdf [password protected].
21. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events (CTCAE) v4.0 [Internet]. Bethesda, MD: National Institutes of Health, National Cancer Institute; 2009 May 28 [cited 2017 Dec 20]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_4.03.xlsx.
22. van Tilburg CM, Bierings MB, Berbers GA, et al. Impact of treatment reduction for childhood acute lymphoblastic leukemia on serum immunoglobulins and antibodies against vaccine-preventable diseases. Pediatr Blood Cancer 2012 May;58(5):701-7. DOI: https://doi.org/10.1002/pbc.23258.
23. Chen SH, Liang DC. Intravenous immunoglobulin prophylaxis in children with acute leukemia following exposure to varicella. Pediatr Hematol Oncol 1992 Oct-Dec;9(4):347-51. DOI: https://doi.org/10.3109/08880019209016606.