haematologica
Journal of the Ferrata Storti Foundation

Immunoglobulin prophylaxis prevents hospital admissions for fever in pediatric acute lymphoblastic leukemia: results of a multicenter randomized trial

by Kirsten A. Thus, Hester A. de Groot-Kruseman, Pauline Winkler-Seinstra, Marta Fiocco, Heidi Segers, Cor van den Bos, Inge M. van der Sluis, Wim J.E. Tissing, Margreet A. Veening, Christian Michel Zwaan, Cornelis M. van Tilburg, Rob Pieters, and Marc Bierings

Received: March 8, 2024.
Accepted: July 29, 2024.

Citation: Kirsten A. Thus, Hester A. de Groot-Kruseman, Pauline Winkler-Seinstra, Marta Fiocco, Heidi Segers, Cor van den Bos, Inge M. van der Sluis, Wim J.E. Tissing, Margreet A. Veening, Christian Michel Zwaan, Cornelis M. van Tilburg, Rob Pieters, and Marc Bierings. Immunoglobulin prophylaxis prevents hospital admissions for fever in pediatric acute lymphoblastic leukemia: results of a multicenter randomized trial. Haematologica. 2024 Aug 8. doi: 10.3324/haematol.2024.285428 [Epub ahead of print]

Immunoglobulin prophylaxis prevents hospital admissions for fever in pediatric acute lymphoblastic leukemia: results of a multicenter randomized trial

Kirsten A Thus,[1] Hester A de Groot-Kruseman,[1] Pauline Winkler-Seinstra,[1] Marta Fiocco,[2] Heidi Segers,[3] Cor van den Bos,[4] Inge M van der Sluis,[5] Wim J E Tissing,[6] Margreet A Veening,[7] Christian Michel Zwaan,[5] Cornelis M van Tilburg,[8] Rob Pieters,[1] Marc Bierings[1]

1: Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

2: Mathematical Institute Leiden University, Leiden University, Leiden, The Netherlands; Department of Biomedical Data Science, Section Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

3: Department of Pediatric Hemato-Oncology, University Hospitals Leuven, Leuven, Belgium

4: Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

5: Department of Pediatric Oncology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

6: Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

7: Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Oncology, Cancer Center Amsterdam, Amsterdam, The Netherlands; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

8: Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany; Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Heidelberg, Germany; German Cancer Consortium (DKTK), Heidelberg, Germany; National Center for Tumor diseases (NCT), Heidelberg, Germany

Acknowledgments

The authors would like to thank all included patients; members of the DCOG ALL-11 protocol committee; research nurses and data managers in the including centers and the DCOG trial office.

Funding

The study was funded by Prothya Biosolutions who supplied the IVIG free of charge and the costs for pharmacy, next to a fee per patient and funding for the data center, and by the Children-Cancer Free foundation (KIKA, project number 110).

Conflict of interests

CMZ received institutional support for clinical trials from Pfizer, Abbvie, Takeda, Jazz, Kura, Gilead, Daichii Sankyo, consulting fees from Kura Oncology, BMS, Novartis,

Gilead, Incyte, Syndax, and participated in data safety monitoring boards or advisory boards of Novartis, Sanofi and Incyte.

CMT participates in advisory boards of Alexion, Bayer and Novartis.

RP participates in advisory boards of Jazz Pharma, and Servier.

MB participates in an Pfizer advisory board.

Authorship

Contribution: KAT analyzed the data and prepared the manuscript; HAGK gathered data and analyzed the data; PWS gathered data; MF analyzed the data; HS gathered data; CCB, IMS, WJET, MAV, CMZ enrolled patients and collected data; CMT, RP and MB designed the study and interpreted data. All authors reviewed, revised, and provided final approval of the manuscript.

Clinical trial details

Trial registration number: EudraCT 2012-000067-25, NL3227

Data sharing agreement

Data sets supporting the results of the completed study, containing unidentifiable data, will be made available after the publication of the final study results within three months from initial request to researchers who provide a methodologically sound proposal. The data will be provided in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Corresponding author

Marc Bierings

Princess Máxima Center for Pediatric Oncology

Heidelberglaan 25

3584 CS Utrecht

the Netherlands

m.b.bierings-2@prinsesmaximacentrum.nl

Abstract

Infections lead to substantial morbidity during treatment of acute lymphoblastic leukemia (ALL) in which the adaptive immune system gets severely affected, leading to declining serum immunoglobulin levels. The aim of this trial was to investigate whether intravenous immunoglobulin (IVIG) prophylaxis in pediatric patients with ALL prevents admissions for fever.

This randomized controlled trial was a subtrial of the national Dutch multicenter ALL study. Patients aged 1-19 years with medium risk (MR) ALL were randomized into two groups receiving either IVIG prophylaxis (0.7 g/kg IVIG given every three weeks, starting day 22 after diagnosis) or well defined standard of care (control group).

Between October 2012 until March 2019, 91 (51%) patients were randomly assigned to IVIG prophylaxis and 86 (49%) to the control arm. In the IVIG prophylaxis group there were 206 admissions for fever versus 271 in the control group (p=0.011). IVIG prophylaxis was not associated with bacteremia. However, IVIG prophylaxis was associated with significantly less admissions for fever with negative blood cultures compared to the control group (N=113 versus 200, p<0.001). The difference in number of admissions for fever was observed specifically during maintenance treatment (N=100 versus 166, p<0.001); resulting in less antibiotic treatments (N=78 versus 137, p<0.001) and less chemotherapy adaptation (N=72 versus 134, p<0.001).

To conclude, in pediatric patients with MR ALL, IVIG prophylaxis was associated with significantly less admissions for fever with negative blood cultures during maintenance treatment, resulting in less antibiotic treatments and chemotherapy adaptations.

Introduction

Infections are an important cause of mortality and morbidity in pediatric patients with acute lymphoblastic leukemia (ALL). In pediatric patients with hematological malignancies, approximately 20% of deaths are treatment related, with infection being responsible for more than half of these deaths.[1-3] Next to mortality risk, there is substantial morbidity of fever often leading to admissions. Moreover, infections may lead to interruption of leukemia treatment, and therefore potentially enhance relapse risk.[4]

During treatment of ALL, the adaptive immune system gets severely affected. This is shown by persistent low B-cell numbers, declining serum immunoglobulin (IgG) levels and low specific antibody levels.[5, 6] Theoretically, one may partially overcome the increased infection risk by supplementing the low IgG levels with intravenous immunoglobulins (IVIG).

In patients with primary immunodeficiency leading to agammaglobulinemia, prophylactic substitution of IVIG is shown to be effective in preventing infections.[7] In adults, it has been shown that IVIG prophylaxis may reduce the number of infections in patients with lymphoproliferative diseases with hypogammaglobulinemia.[8, 9] Currently, it is unknown whether prophylactic administration of IVIG prevents infections during ALL treatment. Since it is an expensive treatment and its administration can lead to adverse events, the value of IVIG for infection prevention during ALL treatment needs to be established.

This trial investigates the role of IVIG prophylaxis in children with newly diagnosed ALL, treated according to the DCOG ALL-11 protocol. It is the first multicenter randomized trial investigating the effect of IVIG in patients with ALL on number of

admissions for fever, blood culture results, adaptations in chemotherapy, and relapse risk.

Methods

Trial design

This multicenter open-label randomized trial was a subtrial of the Dutch multicenter ALL study (DCOG ALL-11, described in detail in the trial register, trial registration number: EudraCT 2012-000067-25, NL3227 (clinicaltrialregister.nl) and in Pieters, et al.,[3]). In this IVIG subtrial, performed across six centers in the Netherlands (described in supplementary data), patients were randomly assigned to IVIG prophylaxis or control group. The trial was conducted in accordance with the Declaration of Helsinki. The study has been approved by the medical ethics committee of the Erasmus Medical Center Rotterdam. Written informed consent was obtained from all study participants and/or their legal guardians.

Endpoints

The primary goal was to evaluate the number of infectious episodes for which patients were admitted. As in practice this means an admission for fever, the primary endpoint was number of admissions for fever. Secondary endpoints were: number of therapeutic antibiotic courses, blood culture results, number of ICU admissions due to fever, number of chemotherapy adaptations due to admission for fever, five year cumulative incidence of relapse, disease free survival (DFS, with event defined as relapse, secondary malignancy or death in remission), and overall survival (OS) from date of diagnosis.

Patients

All patients, aged 1-19 years, in the medium risk (MR) group of the DCOG ALL-11 trial, were considered eligible for inclusion (for detailed in- and exclusion criteria see supplementary data). Randomization was performed at start of ALL treatment, before risk stratification in DCOG ALL-11 was done. When patients were subsequently stratified according to standard or high risk ALL treatment, they went off study.

Procedures

Patients randomized in the IVIG prophylaxis group, started IVIG prophylaxis at day 22 after diagnosis. Patients received 0.7 g/kg/infusion IVIG (Nanogam, Prothya Biosolutions), with a maximum of 50 gram per infusion, every three weeks until 104 weeks of ALL treatment. Details regarding the criteria to start IVIG infusion are described in the supplementary data. If IVIG infusion had to be postponed for an interval of more than eight weeks since the last infusion, the patient was withdrawn from the study.

Patients in the control arm were allowed to receive IVIG treatment under strict criteria (see supplementary data).

Data was gathered in case report files (detailed description in supplementary data). Side effects were documented according to CTCAE criteria version 4.03. Severe adverse events (SAEs) were defined in the DCOG ALL-11 study.

Sample size calculation and statistical analysis

By performing Monte Carlo simulations with 10000 replications, a sample size of 70 patients per arm was estimated to detect a reduction of 50%, with power equal to 80% and one-sided test with alpha 5% (details about the sample size calculation are reported in the supplementary data).

Analyses were performed according to intention-to-treat principle and per-protocol principle (patients that followed IVIG protocol at least one year after diagnosis). Patient characteristics were compared using Pearson Chi Square test for categorical variables and t-test for continuous variables. Due to the presence of overdispersion, a negative binomial regression model was estimated to study the effect of IVIG prophylaxis on outcomes; age as categorical variable was included in all models. The difference in duration of admission was compared using Mann-Whitney U Tests. Cumulative incidence of relapse, DFS and OS were estimated using Kaplan-Meier's methodology. Logrank test was used to compare differences between estimated survival curves. The total percentage of relapse was computed for each group. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed in SPSS version 26 and in R software environment.[10] The library MASS was used to estimate the negative binomial regression model.

Results

Patient characteristics

Patients have been included from October 2012 until March 2019 in this subtrial of DCOG ALL-11. Of the 819 patients included in DCOG ALL-11, 513 patients were considered for randomization in this subtrial. Among these 513 patients, 252 did not consent, therefore ultimately 261 patients were randomized (Figure 1). 182 randomized patients were stratified to the MR group of DCOG ALL-11. Three patients in the intervention group withdrew consent after randomization, but before actual start of IVIG prophylaxis, and two patients were not started on the IVIG trial due to toxicity during ALL induction, therefore ultimately 177 patients (91 in IVIG prophylaxis and 86

in control group) could be included in intention-to-treat analyses. Of these 177 patients, 165 patients (82 in IVIG prophylaxis and 83 in control group) were adherent to the IVIG protocol for at least one year and were included in per-protocol analyses. Three patients in the IVIG group were withdrawn from the study because the interval between IVIG infusions was too long (Figure 1).

There were no significant differences in baseline characteristics between the experimental and control group (Table 1). Seven (4%) patients had IgG levels <4 g/L before start of the IVIG trial. Figure 2 shows IgG levels over time. In the control group, 69 (80%) of patients had IgG levels <4 g/L at some point during treatment and 15 (17%) patients received a total of 48 IVIG infusions. Forty-six (96%) of these infusions were during maintenance treatment. In the study protocol was defined under what conditions patients in the control group could receive IVIG (supplementary data). Unfortunately however, for seven (47%) patients the reason for IVIG substitution was not known, for six (40%) patients the indication was ≥4 admissions for fever, one (7%) patient received IVIG because of an ICU admission and one (7%) because of central nervous system infection.

Safety

In total 122 AEs were reported in 72 patients: 76 in the IVIG prophylaxis group in 40 patients and 46 in the control group in 32 patients (p=0.079, based on negative binomial models, Supplementary Table S1). Only four SAEs were considered (possibly) related to IVIG: two allergic reactions, one fever, and one acute kidney injury two weeks after IVIG infusion. There were significantly more (peripheral and cerebral combined) thromboses in the IVIG prophylaxis group (N=14 in the IVIG prophylaxis group compared to N=2 in the control group, p=0.006).

Admissions for fever

In intention-to-treat analyses, we observed a total of 477 hospital admissions for fever, 206 in the IVIG prophylaxis group and 271 in the control group (p=0.011, Table 2; Figure 3; for estimates of effect see Supplementary Table S2). The majority of admissions was for fever in neutropenia, 127 in the IVIG prophylaxis group and 176 in the control group (p=0.016, Table 2; Figure 3). Patients in the youngest age quartile were more often admitted for fever than patients in the oldest quartile (304 (64%) admissions for fever in patients 1-4 years, 21 (4%) in patients 15-18 years, Supplementary Table S3). Seven of 206 (3%) admissions for fever resulted in ICU admissions in the IVIG prophylaxis and six of 271 admissions (2%) in the control group. The duration of admission was not different amongst the two groups (for IVIG prophylaxis median 4 days, interquartile range 5 days, for the control group median 4 days, interquartile range 3 days, p=0.102).

We next studied in which treatment phase IVIG prophylaxis was most relevant. Specifically during maintenance treatment, there were significantly less admissions for fever in the IVIG prophylaxis group (N=100) compared to the control group (N=166, p<0.001, Table 2; Figure 3). In maintenance phase, IVIG prophylaxis resulted in more than 50% reduction of admissions for fever in neutropenia (N=51 and 108, for IVIG prophylaxis and control group, respectively, p<0.001, Table 2; Figure 3).

To investigate whether the effect of IVIG prophylaxis was influenced by difference in follow-up time in both patient groups, we performed per-protocol analyses. These per-protocol analyses showed similar results: 198 hospital admissions for fever in the IVIG prophylaxis group and 265 in the control group (p=0.024, Table 2; Figure 3).

This difference was also attributed to significantly less admissions for fever in maintenance phase (N=99 in the IVIG prophylaxis group and 164 in the control group, p=0.002, Table 2; Figure 3).

Blood cultures, antibiotics and chemotherapy adaptation

Although the exact cause of fever was highly diverse and mostly not (microbiologically) proven, in 440 (92%) admissions for fever blood cultures were performed. In the majority of admissions for fever, the blood culture was negative (N=313 of 440 blood cultures, 71%). In intention-to-treat analyses, the absolute number of admissions for fever with a positive blood culture was not significantly different in the IVIG prophylaxis group (N=69) compared to the control group (N=58, p=0.419), but detailed results regarding the exact pathogen were often not noted in the CRFs. However, IVIG prophylaxis was associated with significantly less admissions for fever with a negative blood culture (N=113 in the IVIG prophylaxis group and 200 in the control group, p<0.001, Table 2; Figure 3). For the admissions with a negative blood culture, many different causes of fever were reported, the majority being fever of unknown origin or upper respiratory tract infections (N=147 (47%) and 86 (27%), respectively), suggesting a viral infection. When separately analyzing the admissions for fever during maintenance treatment, IVIG prophylaxis was also associated with significantly less admissions for fever with a negative blood culture (N=52 in the IVIG prophylaxis group and 125 in the control group, p<0.001, Table 2; Figure 3).

Patients in the IVIG prophylaxis group received significantly less empirical antibiotic therapy during admission for fever (N=165) compared to the control group (N=212, p=0.030, Table 2; Figure 3). The difference was more pronounced during

maintenance treatment (N=78 in the IVIG prophylaxis and 137 in the control group, p<0.001, Table 2; Figure 3).

The number of adaptations of chemotherapy after admission for fever was significantly less in the IVIG prophylaxis group (N=72) compared to the control group (N=134), during maintenance treatment (p<0.001, Table 2; Figure 3).

In per-protocol analyses, IVIG prophylaxis was associated with significantly less admissions for fever with negative blood cultures as well (N=108 in the IVIG prophylaxis group and 198 in the control group, p<0.001, Table 2; Figure 3), especially in maintenance phase (N=52 in the IVIG prophylaxis group and 125 in the control group, p<0.001, Table 2; Figure 3). IVIG prophylaxis resulted in significantly less empirical antibiotic therapy (N=78 in the IVIG prophylaxis group and 136 in the control group, p<0.001, Table 2; Figure 3), and less adaptation in chemotherapy (N=72 in the IVIG prophylaxis group and 132 in the control group, p<0.001, Table 2; Figure 3) in maintenance phase.

Relapse, DFS and OS

There were seven relapses in the IVIG prophylaxis group and six in the control group; (5-year relapse incidence was 8.4% (3.1%) and 7.5% (3.3%), for IVIG prophylaxis and control group, respectively, Supplementary Figure S1). One patient in the IVIG prophylaxis group died in remission 45 months after diagnosis (due to a complication of stem cell transplantation, off note is that this patient stopped the IVIG trial within three months after diagnosis because the interval between IVIG infusions was too long due to toxicity), and two patients in the control group died (one of bacteremia 9.5 months after diagnosis and one after relapse 54 months after diagnosis). IVIG prophylaxis did not significantly impact 5-year DFS (90.3% (3.3%) and 91.4% (3.4%),

for IVIG prophylaxis and control group, respectively, Supplementary Figure S1) or OS (98.7% (1.3%) and 98.8% (1.2%), for IVIG prophylaxis and control group, respectively, Supplementary Figure S1).

Discussion

This is the first randomized trial investigating IVIG prophylaxis in pediatric ALL patients. Although IVIG prophylaxis did not result in the targeted 50% reduction of admissions for fever overall, IVIG prophylaxis did result in significantly less admissions for fever with a negative blood culture, less empirical antibiotic therapy, and less adaptations of chemotherapy during maintenance treatment. Once patients were admitted for fever, IVIG prophylaxis did not impact the duration of admission and there was no effect on ICU admissions. Although IVIG prophylaxis resulted in less chemotherapy adaptation, there was no significant impact on relapse, DFS and OS. However, the number of relapse was small in this cohort.

A recent retrospective study in pediatric patients with ALL during maintenance therapy, with a small number of patients (63 patients receiving some IgG monitoring/supplementation), did not show a significant impact of IVIG supplementation on febrile episodes.[11] These data are hard to compare to our study, due to the retrospective character and the small size of that study.

IVIG prophylaxis likely prevented viral infections in our patient cohort. There was no difference in the number of positive blood cultures, however there was a significant decrease in admissions for fever with a negative blood culture in the IVIG prophylaxis group. Most admissions for fever with a negative blood culture were attributed to fever of unknown origin and upper respiratory tract infections, indicative for a

reduction in viral infections by IVIG prophylaxis, in line with previous observations in adult patients with lymphoproliferative diseases.[9]

IVIG prophylaxis was well tolerated and not associated with severe side effects, in line with previous observations,[12] although there was a trend for more SAEs in the IVIG prophylaxis group. The study was not set up to analyze specific SAEs separately, however, IVIG prophylaxis was significantly associated with increased risk of thrombosis. For thrombosis, the causal mechanism is hard to define as patients for instance also received asparaginase and glucocorticoids, and have central venous catheters (off note, in the DCOG ALL-11 protocol patients received Vincristine, Dexamethasone pulses throughout maintenance). In our country, it is common practice for patients to keep their central venous catheter throughout maintenance treatment. Our data did not include information on other risk factors for thrombosis such as Factor V Leiden and APC resistance. The majority of 10 out of 16 (62.5%) thrombosis occurred prior to maintenance treatment, suggestive of other risk factors playing a role in the development of thrombosis. Potentially the awareness for thrombosis was biased towards the IVIG group. Nonetheless, thrombosis is a potential side effect of IVIG, that should be kept in mind when prescribing IVIG prophylaxis.

Of note is that 15 (17%) patients in the control group received one or more IVIG infusions (under strict conditions). It is therefore a standard of care control group. Potentially the effect of IVIG prophylaxis might be greater when comparing it to a genuine control group without IVIG.

The fact that the study was not blinded, may theoretically have led to a bias in admitting patients in the control group more often. However, the majority of

admissions were for fever in neutropenia, which is a strict indication for admission. In addition, there was no difference in duration of admission for fever in both groups, suggesting that once admitted, patients were equally ill in both groups. Therefore we believe this potential bias due to non-blinding has not influenced our data considerably.

A drawback of our study is that it was designed with a randomization early within the DCOG ALL-11 protocol, before a large number of patients had developed hypogammaglobulinemia. In our study, only seven (4%) patients had IgG levels <4 g/L before start of the IVIG trial, which is a commonly used cut off for suppletion.[13] Based on these seven patients, we cannot answer whether patients with hypogammaglobulinemia at diagnosis would benefit most from IVIG prophylaxis. However, in this trial, IVIG prophylaxis prevented admissions for fever specifically during maintenance treatment, which is also the period of lowest IgG levels (Figure 2).[5] Potentially, measuring IgG levels during maintenance treatment may be helpful in determining which patients would benefit from IVIG prophylaxis.

The MR group of the DCOG ALL-11 study is the largest risk group including 70% of all patients. In our IVIG trial only MR patients were included. Although a downside of our study is that almost half of the eligible patients did not consent to the trial, we believe the data are generalizable to the entire MR group, as OS and DFS rates are comparable.[3] The advantage of only including MR patients in the study is that this did result in a homogeneous group of patients in which the effect of IVIG could be well studied. A limitation, however, is that this is not a subset of patients with the highest (viral) infection risk. Ultimately, one would like to determine whether IVIG prophylaxis can prevent infections in patients with a high viral infection risk, for example younger patients, patients with trisomy 21, patients within families with young children,

patients with an intensive (high risk) treatment schedule, treatment during winter months and patients that have developed multiple infections previously. Moreover, it would be interesting to study the effect of IVIG prophylaxis in newer more targeted B-ALL therapies resulting in B-cell aplasia and consequently hypogammaglobulinemia, like CAR-T cells and blinatumomab. Setting up a study only randomizing these patients with a high risk of viral infections would however take an extremely long recruitment period.

To conclude, in pediatric patients with MR ALL, IVIG prophylaxis leads to a significant reduction of admissions for fever with negative blood cultures during maintenance treatment, and leads to a decrease in the use of empirical antibiotic therapy and chemotherapy adaptations. As IVIG prophylaxis likely prevents viral infections, our data do not support routine use of IVIG prophylaxis for every ALL patient. However, a subset of patients with a high viral infection risk might benefit from IVIG prophylaxis with less admissions for fever, in maintenance treatment. When prescribing IVIG prophylaxis, clinicians should bear in mind a potential risk of thrombosis.

References

1. Loeffen EAH, Knops RRG, Boerhof J, et al. Treatment-related mortality in children with cancer: Prevalence and risk factors. Eur J Cancer. 2019;121:113-122.
2. Pieters R, de Groot-Kruseman H, Van der Velden V, et al. Successful Therapy Reduction and Intensification for Childhood Acute Lymphoblastic Leukemia Based on Minimal Residual Disease Monitoring: Study ALL10 From the Dutch Childhood Oncology Group. J Clin Oncol. 2016;34(22):2591-2601.
3. Pieters R, de Groot-Kruseman H, Fiocco M, et al. Improved Outcome for ALL by Prolonging Therapy for IKZF1 Deletion and Decreasing Therapy for Other Risk Groups. J Clin Oncol. 2023;41(25):4130-4142.
4. Yeoh A, Collins A, Fox K, et al. Treatment delay and the risk of relapse in pediatric acute lymphoblastic leukemia. Pediatr Hematol Oncol. 2017;34(1):38-42.
5. 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;58(5):701-707.
6. van Tilburg CM, van der Velden VH, Sanders EA, et al. Reduced versus intensive chemotherapy for childhood acute lymphoblastic leukemia: impact on lymphocyte compartment composition. Leuk Res. 2011;35(4):484-491.
7. Quartier P, Debre M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr. 1999;134(5):589-596.
8. Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet. 1994;343(8905):1059-1063.
9. 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;2008(4):CD006501.
10. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2022.
11. Holmes EA, Friedman DL, Connelly JA, Dulek DE, Zhao Z, Esbenshade AJ. Impact of IgG Monitoring and IVIG Supplementation on the Frequency of Febrile Illnesses in Pediatric Acute Lymphoblastic Leukemia Patients Undergoing Maintenance Chemotherapy. J Pediatr Hematol Oncol. 2019;41(6):423-428.
12. 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.
13. Foster JH, Cheng WS, Nguyen NY, Krance R, Martinez C. Immunoglobulin prophylaxis in pediatric hematopoietic stem cell transplant. Pediatr Blood Cancer. 2018;65(12):e27348.

Tables

Table 1: Baseline characteristics.

	IVIG, N (%)	Control, N (%)	p-value
N	91	86	
Gender			0.763
Male	53 (58)	52 (61)	
Female	38 (42)	34 (40)	
Age in categories			0.798
1-4 years	42 (46)	35 (41)	
5-9 years	25 (28)	29 (34)	
10-14 years	14 (15)	14 (16)	
15-18 years	10 (11)	8 (9)	
White Blood cell count in categories			0.557
<25 *10^9/L	67 (74)	61 (71)	
25-50 *10^9/L	10 (11)	7 (8)	
>50 *10^9/L	14 (15)	18 (21)	
Phenotype			0.131
B-lineage	83 (91)	72 (84)	
T-lineage	8 (9)	14 (16)	
NCI risk group / lineage			0.320
B-lineage NCI Standard Risk	55 (60)	48 (56)	
B-lineage NCI High Risk	28 (31)	24 (28)	
T-lineage	8 (9)	14 (16)	
CNS status (in CSF)			NA
CNS1	41 (45)	33 (38)	
CNS2	35 (39)	40 (47)	
CNS3	0 (0)	3 (4)	
TLP+	9 (10)	7 (8)	
TLP-	3 (3)	0 (0)	
Inconclusive/Not done	3 (3)	3 (4)	
Genetic subtype			NA
ETV6::RUNX1	21 (23)	19 (22)	
KMT2A rearranged	1 (1)	0 (0)	
TCF3::PBX1	1 (1)	2 (2)	
High Hyperdiploid (51-65)	24 (26)	13 (15)	
T-other	6 (7)	12 (14)	
B-other	25 (28)	32 (37)	
Missing ploidy data	13 (14)	8 (9)	
IgG level at diagnosis in g/L (mean ± SD)	8.3 ± 2.4	9.1 ± 2.7	0.437

Table 2: Comparison of outcomes for the IVIG prophylaxis and control group, overall and during maintenance treatment separately.

Outcome, number of episodes	Overall			Maintenance phase		
	IVIG	Control	p-value	IVIG	Control	p-value
Intention-to-treat analyses						
Admissions for fever	206	271	0.011	100	166	<0.001
Fever in neutropenia	127	176	0.016	51	108	<0.001
Negative blood cultures	113	200	<0.001	52	125	<0.001
Empirical antibiotic therapy	165	212	0.030	78	137	<0.001
Adaptation in chemotherapy	123	185	0.003	72	134	<0.001
Per-protocol analyses						
Admissions for fever	198	265	0.024	99	164	0.002
Fever in neutropenia	126	173	0.040	51	107	<0.001
Negative blood cultures	108	198	<0.001	52	125	<0.001
Empirical antibiotic therapy	158	208	0.029	78	136	<0.001
Adaptation in chemotherapy	119	181	0.005	72	132	<0.001

P-values are based on negative binomial models including age of the patient.

Figure legends

Figure 1: Consort diagram

Figure 2: IgG levels for IVIG prophylaxis and control group

Mean IgG levels and 95%-confidence intervals (g/L) were higher for IVIG prophylaxis in orange compared to control group in blue, as displayed over three weekly intervals. IgG levels for the control group were censored after IVIG substitution. The grey area indicates an IgG level ≤4 g/L which is commonly used as cut-off for substitution. Below the numbers of measured IgG levels per group at several time points are displayed.

Figure 3: Admissions for fever and fever in neutropenia; with negative blood cultures, empirical antibiotic therapy, or chemotherapy adaptation for IVIG prophylaxis and control group

A: intention-to-treat analyses, B: per-protocol analyses. On the Y-axis number of episodes for IVIG prophylaxis patients in orange versus control in blue. Filled bars are before maintenance treatment of ALL, open bars are during maintenance treatment of ALL. P-values are based on negative binomial-models including age of the patient. *: $p<0.05$, **: $p<0.01$ for analyses during entire ALL treatment; #: $p<0.05$, ##: $p<0.01$ for analyses during maintenance phase of ALL treatment separately.

Figure 1

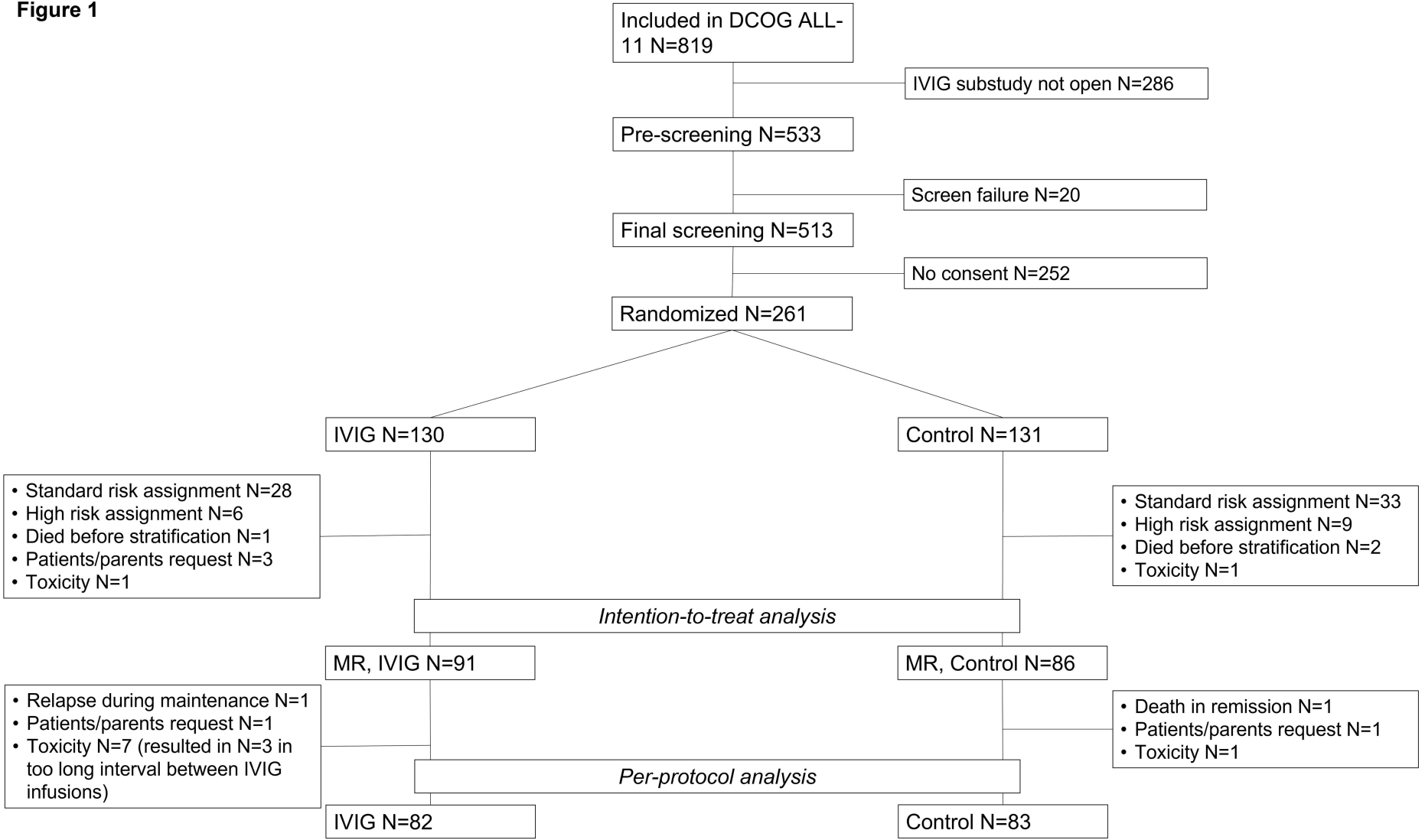
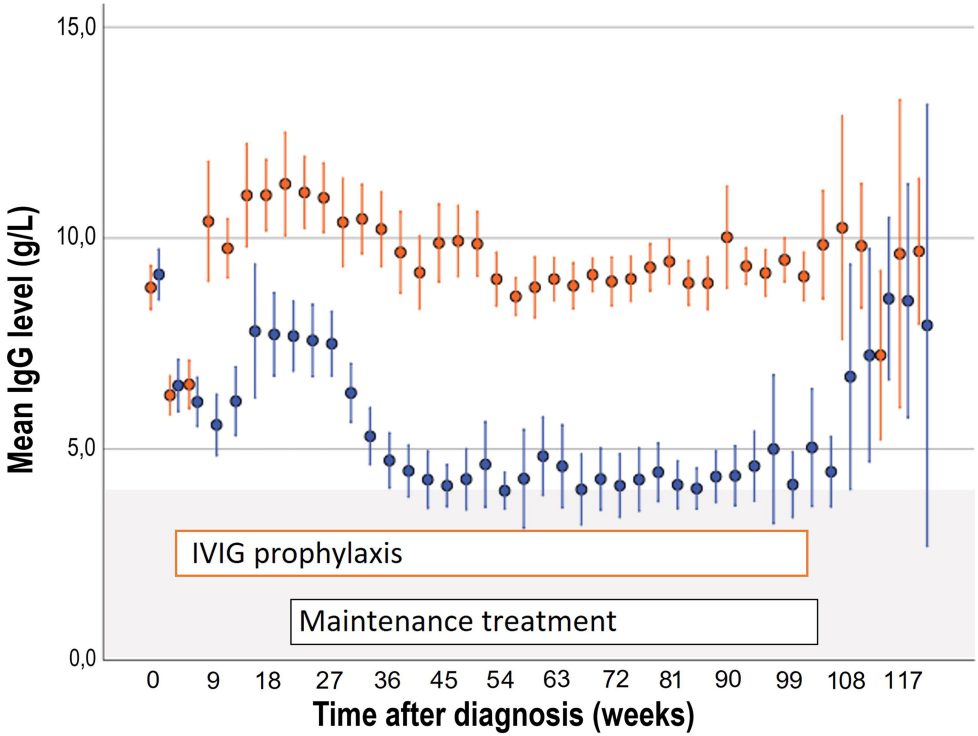
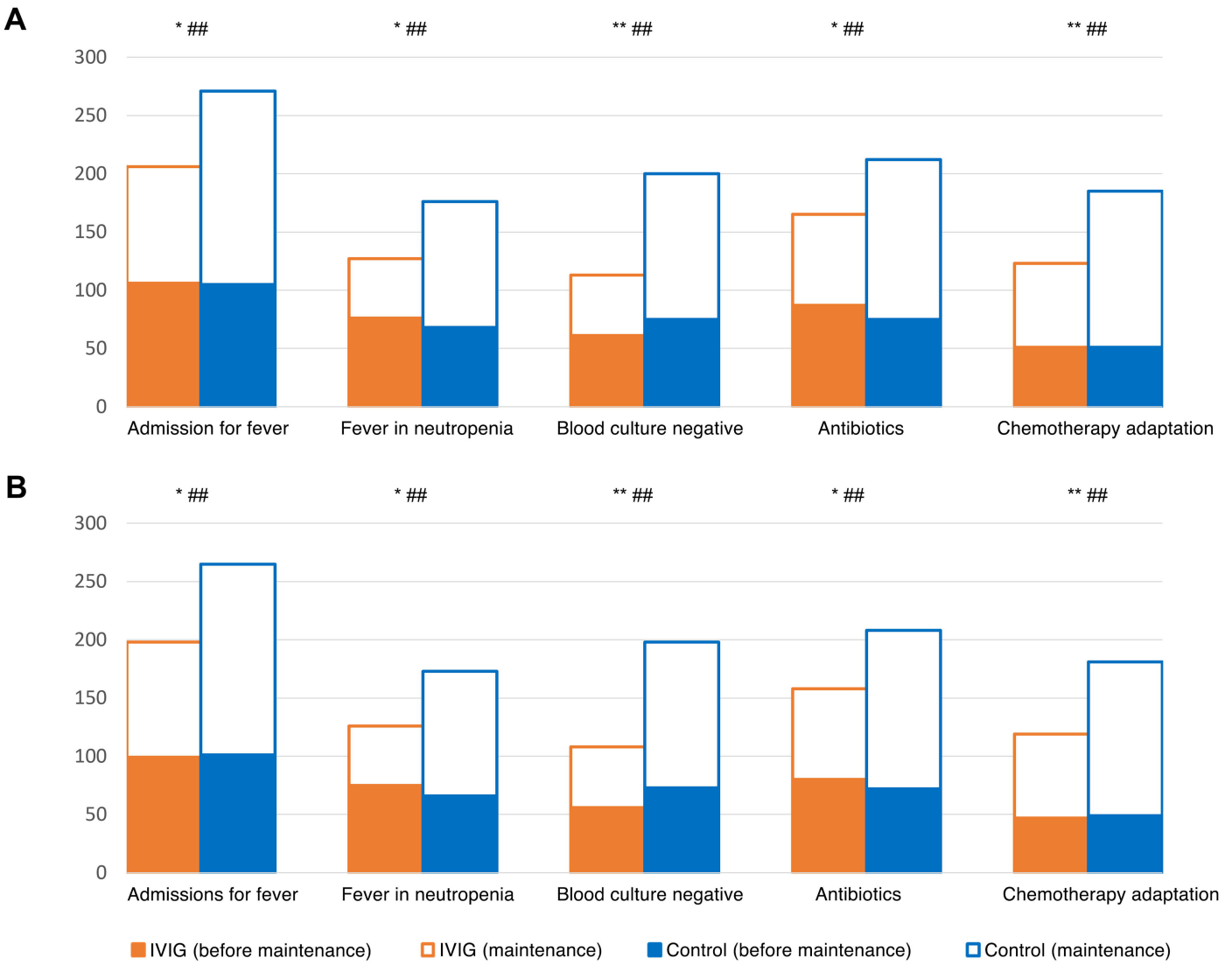

Included in DCOG ALL-11 N=819
IVIG substudy not open N=286
Pre-screening N=533
Screen failure N=20
Final screening N=513
No consent N=252
Randomized N=261
IVIG N=130
Control N=131
• Standard risk assignment N=28
• High risk assignment N=6
• Died before stratification N=1
• Patients/parents request N=3
• Toxicity N=1
• Standard risk assignment N=33
• High risk assignment N=9
• Died before stratification N=2
• Toxicity N=1
Intention-to-treat analysis
MR, IVIG N=91
MR, Control N=86
• Relapse during maintenance N=1
• Patients/parents request N=1
• Toxicity N=7 (resulted in N=3 in too long interval between IVIG infusions)
• Death in remission N=1
• Patients/parents request N=1
• Toxicity N=1
Per-protocol analysis
IVIG N=82
Control N=83

Figure 2



IVIG prophylaxis	87	36	56	51	39	53	40	52	43	53	44	50	13	7
Control	81	30	42	39	39	36	23	31	23	30	18	21	7	7

Figure 3


A
* ##
* ##
** ##
* ##
** ##
300
250
200
150
100
50
0
Admission for fever
Fever in neutropenia
Blood culture negative
Antibiotics
Chemotherapy adaptation
B
* ##
* ##
** ##
* ##
** ##
300
250
200
150
100
50
0
Admissions for fever
Fever in neutropenia
Blood culture negative
Antibiotics
Chemotherapy adaptation
IVIG (before maintenance)
IVIG (maintenance)
Control (before maintenance)
Control (maintenance)

Supplementary data

Study centers

Vrije Universiteit University Medical Center, Amsterdam

Amsterdam University Medical Center, Emma Children's hospital, Amsterdam

University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht

University Medical Center Groningen, Beatrix Children's Hospital, Groningen

Erasmus Medical Center, Sophia Children's Hospital, Rotterdam

Princess Máxima Center for Pediatric Oncology, Utrecht

Definition of MR group, in- and exclusion criteria

MR was defined as patients with newly diagnosed ALL with minimal residual disease (MRD) positivity based on molecular assays, at day 33 and/or day 79 of treatment, but MRD at day 79 of treatment $<10^{-3}$, or in case of either inconclusive/missing MRD results, and absence of high risk criteria.[3] Exclusion criteria were: underlying immune deficiency present before diagnosis of ALL, history of anaphylactic reactions to plasma products, IgA deficiency, history of thrombo-embolism, trisomy 21, fungal infections diagnosed before start of treatment with IVIG, history of renal insufficiency, patients with parents who are not able to understand or answer the questionnaires, pregnancy or unwillingness to use adequate contraceptive measures in females with child bearing potential.

Starting criteria for IVIG infusion

Clinical criteria that had to be met before every IVIG infusion, were: absence of clinical signs of renal failure, absence of diabetic ketoacidosis, absence of acute thrombo-embolic problems, no post-surgery immobilization, absence of clinical signs

of respiratory or circulatory insufficiency, no use of loop diuretics. In case of fever (defined as temperature ≥38.5^{o}C), IVIG infusion was postponed on the first day of fever. In case that IVIG infusion had to be postponed for clinical reasons, IVIG infusion was postponed until the clinical condition of the patient had recovered at the judgement of the treating physician. In case of repeatedly high serum IgG levels (>16 g/L), IVIG dose was decreased with 50% until levels <10 g/L were reached, then the starting dose of 0.7 g/kg was reintroduced.

Criteria for IVIG in control group

When there was an IgG level ≤6 g/L in the first 19 weeks of ALL MR therapy, or ≤4 g/L thereafter, in combination with either one of the following: history of ≥4 admissions for infection; or 1 central nervous system infection; or 1 infection requiring ICU admission, patients in the control group were allowed to receive IVIG. After receiving IVIG once, a new indication occurred when there was an IgG level ≤6 g/L (or ≤4 g/L after 19 weeks of MR therapy) in combination with a history of ≥2 admissions for infection; or 1 central nervous system infection; or 1 infection requiring ICU admission.

Data collection

Hospital records were checked against a parental study diary registering fever episodes in order not to miss any admissions for fever. Subsequently, detailed information of the admissions for fever was recorded in case report forms (CRFs): blood culture results, suspected cause of fever, start of empirical antibiotic therapy, chemotherapy adaptation in relation to the admission for fever, and ICU admission. Chemotherapy adaptation was defined as chemotherapy disrupted or dosage decreased because of this admission for fever. IgG levels were measured before start of the trial and at regular intervals thereafter.

Sample size calculation

A negative binomial distribution was used to compute the number of patients needed to detect a reduction of 50% admissions for fever, since the distribution for admissions for fever shows overdispersion (known from DCOG ALL-10 study[2]). Monte Carlo simulations with 10000 replications yielded 70 patients per arm with power equal to 80% and one-sided test with alpha 5%. Details about the power analysis are reported in the protocol (trial registration number: EudraCT 2012-000067-25, NL3227 (clinicaltrialregister.nl)).

Supplementary table S1: Reported adverse events for the IVIG prophylaxis and control group.

(S)AE	IVIG	CTCAE grade	Control	CTCAE grade
Allergic reaction/Anaphylaxis	2	III-IV	1	IV
Gastro-intestinal toxicity	17	III-IV	13	I-IV
Gastrointestinal bleeding	1		0	
Gastrointestinal colitis	0		1	
Gastrointestinal constipation	1		1	
Gastrointestinal diabetes	1		3	
Gastrointestinal other	1		1	
Gastrointestinal pancreatitis	10		3	
Gastrointestinal perforation	1		0	
Liver failure	1		2	
Veno-occlusive disease	1		2	
Infections	17	III-IV	14	III-V
Infection bacterial	5		5	
Infection fungal	7		7	
Infection pneumocystis jerovecii (carini)	3		1	
Infection unknown origin	2		0	
Infection viral	0		1	
Neurotoxicity	14	II-IV	8	II-IV
Central neurotoxicity convulsion	5		3	
Central neurotoxicity encephalopathy	4		3	
Central neurotoxicity other	3		2	

Peripheral neurotoxicity	2		0	
Thrombosis	14	II-IV	2	III-IV
Thrombosis cerebral	7		2	
Thrombosis peripheral	7		0	
Other	12	II-IV	8	II-IV
Bleeding	1		0	
Electrolyte disorder	2		0	
Fracture	0		1	
Hypertension	0		2	
Hypoglycemia	4		1	
Kidney failure	1		0	
Other	4		3	
Pneumothorax	0		1	
Total	76		46	

Supplementary Table S2

Estimates regression coefficient, adjusted for age, of effect of IVIG on outcomes, obtained with a negative binomial model.

	Overall			**Maintenance phase**		
Outcome	**Coefficient**	**Standard Error**	**p-value**	**Coefficient**	**Standard Error**	**p-value**
Intention-to-treat analyses						

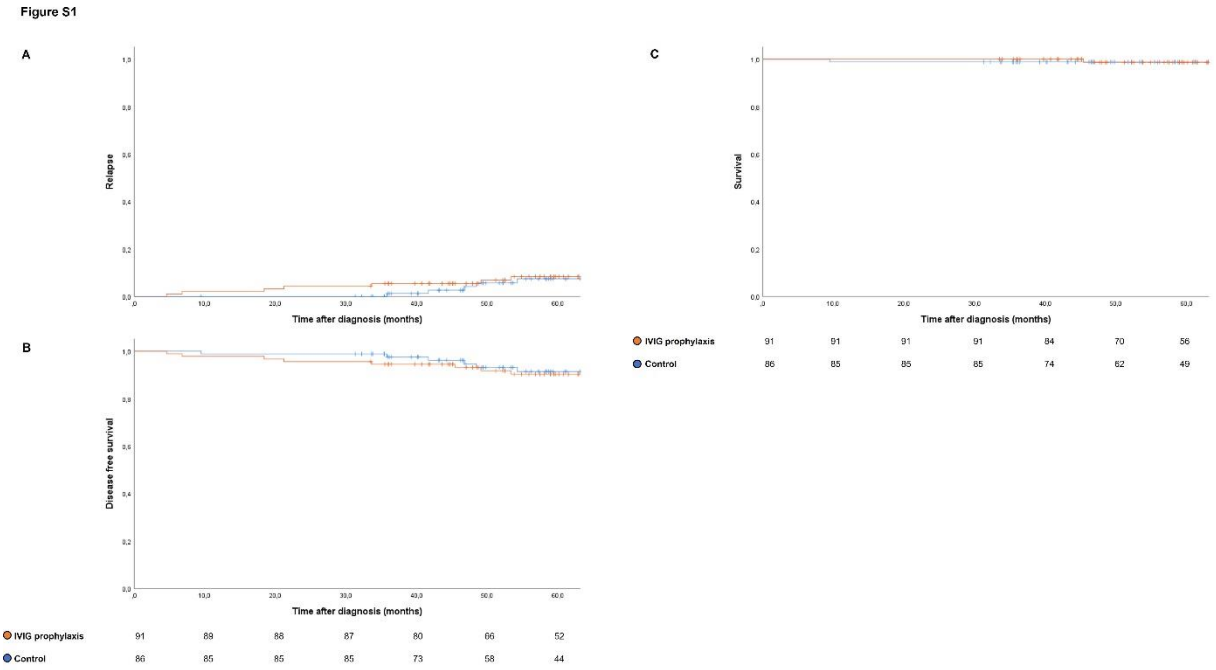
Admissions for fever	-0.321	0.126	0.011	-0.566	0.168	<0.001
Fever in neutropenia	-0.359	0.149	0.016	-0.814	0.207	<0.001
Negative blood cultures	-0.624	0.152	<0.001	-0.951	0.209	<0.001
Empirical antibiotic therapy	-0.298	0.134	0.030	-0.626	0.188	<0.001
Adaptation in chemotherapy	-0.456	0.154	0.003	-0.675	0.197	<0.001
Per-protocol analyses						
Admissions for fever	-0.299	0.132	0.024	-0.541	0.172	0.002
Fever in neutropenia	-0.312	0.155	0.040	-0.800	0.212	<0.001
Negative blood cultures	-0.618	0.159	<0.001	-0.884	0.215	<0.001
Empirical antibiotic therapy	-0.313	0.144	0.029	-0.638	0.192	<0.001
Adaptation in chemotherapy	-0.447	0.159	0.005	-0.669	0.200	<0.001

Supplementary Table S3

Estimates regression coefficient, for different age groups on admissions for fever, obtained with a negative binomial model.

Outcome	Overall			Maintenance phase		
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value
Intention-to-treat analyses						
Age 1-4 years	reference					
Age 5-9 years	-0.615	0.145	<0.001	-0.760	0.193	<0.001
Age 10-14 years	-1.150	0.214	<0.001	-1.473	0.308	<0.001
Age 15-18 years	-1.188	0.265	<0.001	-1.527	0.386	<0.001
Per-protocol analyses						
Age 1-4 years	reference					
Age 5-9 years	-0.608	0.149	<0.001	-0.759	0.192	<0.001
Age 10-14 years	-1.273	0.234	<0.001	-1.603	0.332	<0.001
Age 15-18 years	-1.271	0.299	<0.001	-1.456	0.405	<0.001

Supplementary Figure S1



Relapse (A), Disease free survival (B), and Overall survival (C) curves for IVIG prophylaxis in orange and control group in blue. Relapse was not corrected for competing events, as there was only one death without relapse.