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Acute non-hematological toxicity of intensive chemotherapy of acute lymphoblastic leukemia in children

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Abstract

Introduction: Leukemia belong to 31% of all childhood malignancies. Acute lymphoblastic leukemia (ALL) is the most frequent type of pediatric leukemia accounting for 80–85% of all cases. Progress in diagnostics and therapy of leukemia is dependent on international cooperation. The objective of the study was the analysis of non-hematological toxicity during intensive chemotherapy according to two consecutive intercontinental protocols. Patients and methods: A total number of 210 children diagnosed for ALL who were treated in single center between 2002 and 2018 were divided in two groups defined by therapeutic protocol: ALL IC-BFM 2002 (group 1) and ALL IC-BFM 2009 (group 2). Data were entered prospectively from 2002 into international ALL IC-BFM 2002 and ALL IC-BFM 2009 registry. Non-hematological toxicity was analyzed according to the criteria followed in protocols, compatible with CTCAE criteria. Results: The most frequent toxicities included hepatic toxicity with transaminitis and hyperbilirubinemia, infections, oral mucositis and gut toxicity with vomiting, and/or diarrhea. Non-hematological toxicity episodes calculated as a ratio per patient were comparably often observed in both the groups; however, the distribution was different. There were more grade III and less grade II toxicities. This was mainly related to significant increase in the rates of infections and transaminitis. However, there was a significant decrease in vomiting and central and peripheral neurotoxicity. Conclusions: Intensive treatment of ALL is burdened with frequent severe toxic and infectious complications. Further progress in therapy of pediatric ALL is dependent on sophisticated supportive therapy and very well experienced and knowledgeable therapeutic team.

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Keywords:
acute lymphoblastic leukemia, chemotherapy, toxicity, children

Introduction

Malignant diseases are the second cause of deaths in children, next to accidents and intoxications. Leukemia is the most frequent pediatric neoplastic disease responsible for approximately 26–31% of all childhood malignancies. Acute lymphoblastic leukemia (ALL) is the most frequent type of pediatric leukemia constituting 80–85% of all cases [1]. Progress in diagnostics and therapy for leukemia has led to the cure rate of 70–80% in the beginning of 21st century, compared to <1% in the 1960s of the 20th century [2, 3]. Due to the rarity of the disease, children with ALL are usually treated according to the international protocols [4, 5].

Intercontinental program ALL-IC-BFM 2002 was approved on February 23, 2002, in Hannover by working groups from 10 countries (Argentina, Chile, Croatia, Czech Republic, Hong-Kong, Hungary, Israel, Poland, Ukraine, and Uruguay) [6, 7]. Taking into account the intercontinental character of the project, it was the largest ever study in the entire history of pediatrics in 2002. Children with ALL in Poland from the year 2002 were treated according to Intercontinental Cooperative ALL-IC-2002 protocol up to the year 2011; and then up to 2018 according to ALL-IC-2009 protocol. In children with ALL, treatment with intensive multiagent chemotherapy is complicated due to the toxicities and complications in approximately 70% of patients, regardless of the risk group [8].

Intensive multiagent chemotherapy used in therapy of childhood ALL might be complicated with gastrointestinal toxicity, hepatotoxicity, hypersensitivity reactions to L-asparaginase, asparaginase-associated pancreatitis, hyperlipidemia, osteonecrosis, hypertension, posterior reversible encephalopathy syndrome, seizures, loss of consciousness, methotrexate-associated neurotoxicity, polyneuropathy, sinusoidal obstruction syndrome, thrombosis, pneumonia, and other infections [9]. The profile of toxicities after multidrug chemotherapy in ALL is very wide and also includes many rare complications, such as intestinal perforation [10]. Hypersensivity asparaginase-associated reactions include silent inactivation, skin rash, and abdominal reactions such as abdominalgia and vomiting [11]. Pancreatitis usually is not life-threatening but might lead to delays in chemotherapy, thus increasing the risk of leukemic relapse. Osteonecrosis, hypertension, and hyperlipemia are associated with the use of steroids. These complications can lead to late cardio-vascular disease, thrombolytic sequelae, or pathological fractures [12]. The objective of the study was the analysis of non-hematological toxicity of intensive chemotherapy in children treated for ALL between 2002 and 2018 with two consecutive Intercontinental Cooperative protocols in single center study.

Patients

A total number of 210 patients aged below 18 years at diagnosis, with ALL, were treated in our department between October 1, 2002, and September 30, 2018, with the last follow-up on March 31, 2019. Patients were divided into two groups defined by therapeutic protocol:

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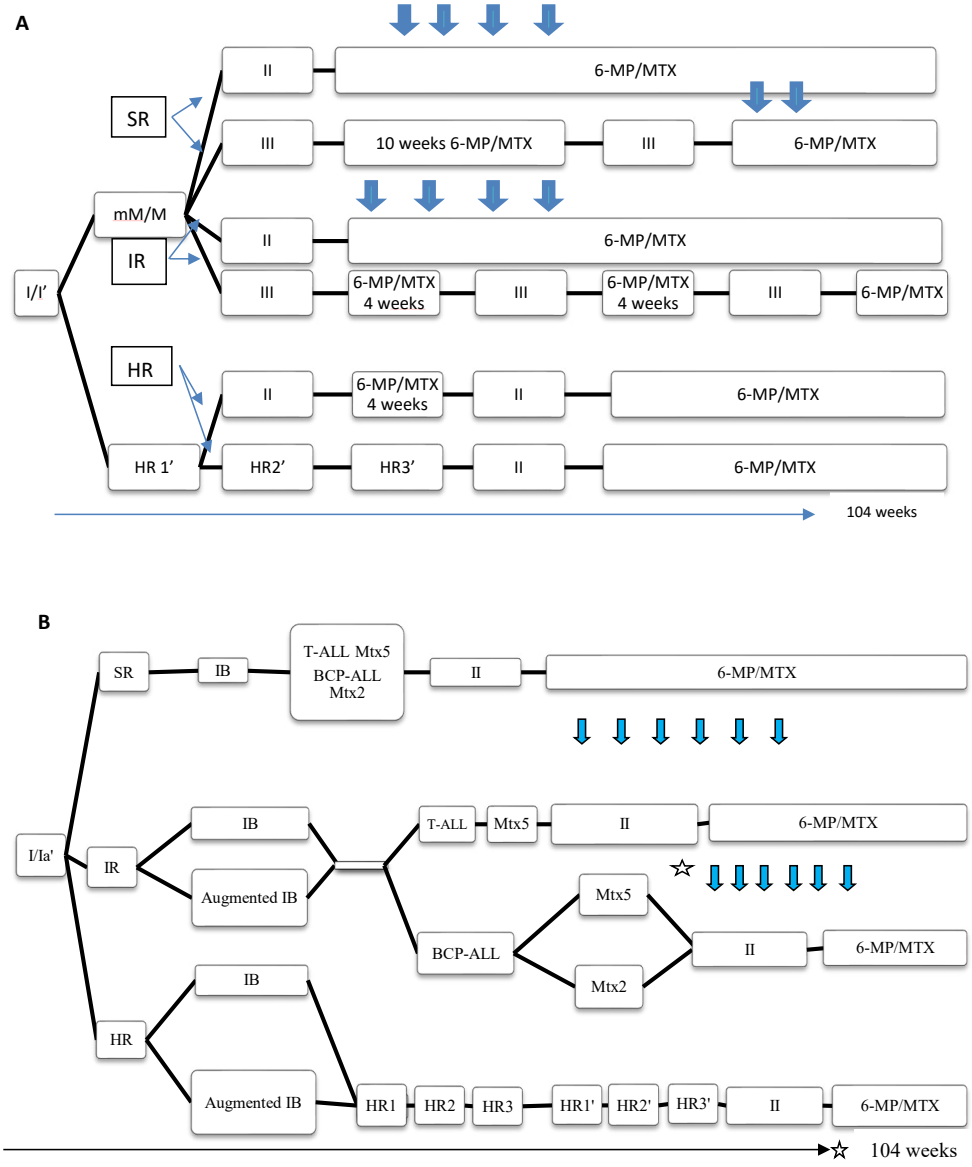
ALL-IC-BFM 2002 (group 1) or ALL-IC-BFM 2009 (group 2). Children aged <1 year were treated with Interfant-06 protocol and children with mature B-cell ALL were excluded from the study.

Group 1 included 115 patients treated between October 1, 2002, and October 31, 2011, according to ALL IC-BFM 2002 protocol, with median follow-up of 7.0 years (range: 0.1–14.2). Group 2 included 95 patients treated between November 1, 2011, and September 30, 2018, according to ALL IC-BFM 2009 protocol, with median follow-up of 3.0 years (range: 0.1–8.3).

Patients were treated according to ALL IC-BFM 2002 protocol "A Randomized Trial of the I-BFM-SG for the Management of Childhood Non-B Acute Lymphoblastic Leukemia, Final Version of Therapy Protocol from May 3, 2002 (Hannover, Germany)" (Fig. 1A) and protocol ALL IC-BFM 2009, "A Randomized Trial of the I-BFM-SG for the Management of Childhood Non-B Acute Lymphoblastic Leukemia Final Version of Therapy Protocol from August-14-2009 (Hannover, Germany)" (Fig. 1B).

Diagnosis of ALL was made according to the criteria presented in therapeutic protocols and was based on conventional diagnostics: bone marrow, peripheral blood, and cerebrospinal fluid smear, as well as flow cytometry results of lymphoblasts immunophenotyping and cytogenetic and molecular results. The database was created according to the data of the in-patient and out-patient charts.

This was a retrospective study, approved by Local Bioethical Committee (KB/590/2018; 25.09.2018); however, data were retrieved from the database prepared prospectively for the international ALL-IC-BFM 2002 and ALL-IC-BFM 2009 registry.



- IT MTX; ☆ Radiotherapy; I//Ia/IB/II/III/Augmented IB/HR1/HR2/HR3 – cycles/subprotocols of chemotherapy; 6MP – mercaptopurine; MTX – methotrexate (2 or 5 g/m^2)

Fig. 1. Scheme of therapy protocol: (A) ALL IC-BFM 2002; (B) ALL IC-BFM 2009

Methods

Design of the study

The study included analysis of non-hematological toxicity, which was analyzed according to the requirements of respective therapeutic protocols, strictly based on criteria NCI CTC (National Cancer Institute Common Toxicity Criteria), adopted by SIOP (The International Society of Paediatric Oncology) and modified by GPOG (German Society of Pediatric Oncology/Hematology) (ALL IC-BFM 2009). The criteria included patient status, organ toxicity, and infectious episodes (Tab. I). In this study, grades II–IV of the disease were analyzed, as they are clinically significant.

Principles of ALL-IC-2002 protocol

Patients stratification in the protocol ALL-IC-BFM 2002 was based on the following factors: age at diagnosis, initial number of leukocytes, early response at day to therapy, two genetic markers t(9;22) and t(4;11), and/or their molecular markers (BCR/ABL and MLL/AF4). Early response to therapy was determined by response to steroid treatment at day 8, and bone marrow response at days 15 and 33. According to these criteria, three risk groups were defined as standard (SR), intermediate (IR), and high (HR) [6, 7].

Standard risk group criteria included <1,000 blasts/mm^3 in peripheral blood on day 8 of induction therapy; age on diagnosis between 1 and 6 years; initial white blood cell count <20,000/mm^3; bone marrow M1/

Table I. Classification of non-hematological toxicity

Grade	0	1	2	3	4
General condition	Normal activity	Mild impairment	Age-related activities strongly limited	Bedridden, in need of nursing	In need of nursing, very sick
Infections					
Infection	None	Mild	Pathogen not identified, IV antibiotics	Pathogen identified, IV antibiotics	Septic shock
Fever (°C)	<38	38–39	>39–40	>40°C; for <24 hours	<40°C; for >24 h
Gastrointestinal toxicity					
Nausea	None	Adequate food intake	Markedly decreased food intake	Almost no food intake	TPN necessary
Vomiting (per day)	0	1	2–5	6–10	>10; TPN necessary
Stomatitis	None	Painless ulceration, erythema	Painful ulceration, can still eat	Painful ulceration, cannot eat	TPN required due to stomatitis
Diarrhea (stool frequency/day)	None	2–3	4–6, or night stools or light cramps	7–9 or incontinence or strong cramps	≥10 or bloody diarrhea or TPN required
Liver toxicity					
Bilirubin concentration	Normal (N) for age	>N – 1.5 × N	>1.5 × N – 3.0 × N	>3.0 × N – 10.0 × N	>10.0 × N
ALT/AST activity	Normal for age	>N – 2.5 × N	>2.5 × N-5.0 × N	>5.0 × N – 20.0 × N	>20.0 × N
Renal toxicity					
Creatinine	Normal for age	>N – 1.5 × N	>1.5 × N – 3.0 × N	>3.0 × N – 6.0 × N	>6.0 × N
Proteinuria (g/L)	None	<3.0	3.0–10.0	>10.0	Nephrotic syndrome
Hematuria	None	Microscopic	Macroscopic w/o clots	Macroscopic with clots	Transfusion required
Creatinine clearance (ml/min/1,73m^2)	≥90	60–89	40–59	20–39	≤19
Cardiac toxicity					
Arrhythmia	None	Asymptomatic, no therapy	Recurrent, persistent, no therapy	Therapy required	Hypotension, ventricular arrhythmia, defibrillation
Cardiac function	Normal for age	EF↓ < 20% baseline value	EF↓ ≥ 20% baseline value	Mild cardiac Insufficiency, therapeutically compensated	Severe/refractory cardiac insufficiency
ECHO: LVSF	≥30%	>24–30%	>20–24%	>15–20%	≤15%
Neurologic toxicity					
Central neurotoxicity	None	Transient lethargy	Somnolence < 50% of the day, moderate disorientation	Somnolence ≥ 50% of the day, disorientation, hallucinations	Coma, seizures
Peripheral neurotoxicity, myopathy	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Unbearable paresthesias, marked motor deficits	Paralysis
Skeletal toxicity					
Osteonecrosis	None	Asymptomatic and detectable only by imaging techniques	Symptomatic with decreased function, but no limitations in everyday living	Symptomatic and restrictions in everyday living	Symptomatic, crippling

LVSF – left-ventricle shortening fraction

M2 on day 15 of induction therapy, and bone marrow M1 on day 33 of induction therapy. All criteria must be fulfilled.

Intermediate risk group criteria included <1,000 blasts/mm^3 in peripheral blood on day 8 of induction therapy; age on diagnosis between 1 and 6 years and/or initial white blood cell count <20,000/mm^3; bone marrow M1/M2 on day 15 of induction therapy, and bone marrow M1 on day 33 of induction therapy; or standard risk group criteria but bone marrow M3 on day 15 of induction therapy, and bone marrow M1 on day 33 of induction therapy.

High risk group criteria included intermediate risk group and M3 on day 15 (but not SR and M3 on day 15); ≥1,000 blasts/mm^3 in peripheral blood on day 8 of induction therapy; bone marrow M2/M3 on day 33 of induction therapy; translocation t(9;22) [BCR/ABL] or t(4;11) [MLL/AF4]. At least one of these criteria must be fulfilled.

Principles of ALL-IC-2009 protocol

Principles of ALL IC-BFM 2009 protocols were similar to the previous one, with stratification into three risk groups. Presence of minimal residual disease (MRD) was added as a new potent stratifying factor. MRD was determined by flow cytometry (FC) immunophenotype analysis on day 15 of induction therapy. Patients stratification in the protocol ALL IC-BFM 2009 was based on the following factors: age at diagnosis, initial number of leukocytes, early response at day to therapy, presence of MRD, two genetic markers t(9;22) and t(4;11), and/or their molecular markers (BCR/ABL and MLL/AF4). Early response to therapy was determined by response to steroid treatment at day 8, and bone marrow response at day 15 and 33. According to these criteria, three risk groups were defined: standard (SR), intermediate (IR), and high (HR).

Standard risk group criteria included <1,000 blasts/mm^3 in peripheral blood on day 8 of induction therapy; age on diagnosis between 1 and 6 years; initial white blood cell count <20,000/mm^3; MRD <0,1% or bone marrow M1/M2 on day 15 of induction therapy, and bone marrow M1 on day 33 of induction therapy. All criteria must be fulfilled.

High risk group criteria included IR and FC MRD > 10% or M3 on day 15; SR and FC MRD >10%; ≥1,000 blasts/mm^3 in peripheral blood on day 8 of induction therapy; bone marrow M2/M3 on day 33 of induction therapy; translocation t(9;22) [BCR/ABL] or t(4;11) [MLL/AF4], and hypodiploidy ≤44 chromosomes. At least one criterion must be fulfilled. Intermediate risk group included all other patients (non-SR and non-HR).

The therapeutic modifications in the protocol, in comparison to the previous one, included increase of the methotrexate dose from 2 g/m^2 to 5 g/m^2 in IR group of B-cell precursor ALL (BCP-ALL), and in T-ALL SR and IR group. In HR group, early intensification Augmented IB protocol was used (with additional 4 doses of vincristine and 12 doses of L-asparaginase). Prophylactic CNS radiotherapy of 12 Gy was designed only for IR patients with T-ALL and initial WBC > 100,000/ml, and HR patients not qualified for allo-HSCT, with the exception of BCP-ALL only due to PPR (prednisolone poor response).

Statistical analysis

Categorical variables were compared to the chi-square test, and non-categorical variables were compared to the Mann–Whitney U test. All reported *p*-values are two-sided; $p < 0.05$ was considered as statistically significant.

Results

Children in group 2 were younger, more often had hyperdiploidy and more often had hypodiploidy, more often had poor prednisolone response by day 8 of induction therapy, and there was a higher rate of High Risk Group patients in group 2 (Tab. II).

In group 1, overall 949 toxic episodes were noted, including 588 of grade II (average 5.11 episodes per patient), 271 grade III (2.36/patient), 90 grade IV (0.78/patient) (Tab. III). Infectious complications were most frequent with the total of 240, including 136 grade II, 90 grade III, and 14 grade IV. Transaminitis was the second most frequent complication, occurring as 216 episodes: 97 grade II, 105 grade III, and 14 grade IV. Other toxicities included vomiting in 96 cases, mucositis in 75 cases, worsening of overall condition in 72 cases, diarrhea in 43 cases, elevated bilirubin serum concentration in 43 cases, and peripheral neuropathies in 30 cases. Rare complications included neurotoxicity and cardiotoxicity.

In group 2, a total number of 724 toxic episodes were observed, including 399 grade II (4.2 episodes per patient), 268 grade III (2.82/patient), and 57 grade IV (0.6/patient). Compared to previous protocol, transaminitis was the most frequent complication, occurring as 259 episodes (106 grade II, 139 grade III, and 14 grade IV), and followed by infectious complications in 271 episodes (158 grade II, 108 grade III, and 5 grade IV). Other complications included mucositis in 78 cases and elevated bilirubin serum concentration in 40 cases. Cardiotoxicity and neurotoxicity occurred rarely.

In the group 2, the rate of episodes of toxicities per 1 patient was comparable to group 2; however, the distribution was different: there were more grade III and less grade II toxicities. This was mainly related to significant increase in rates of infections and transaminitis. However, there was significant decrease in vomiting and neurotoxicity, both central and peripheral (Tab. III).

Discussion

ALL is the most frequent pediatric malignancy. Results of treatment of ALL is regarded as an indicator of level of oncological care and management at local, national, and international level. Due to the relative rarity of pediatric malignancies, most of them is treated in international cooperation. Progress in management of ALL is based on the improvement of multiagent chemotherapy protocols. From the 1970s of the 20th century, children with ALL in Poland are treated with the use of American or German protocols in all pediatric oncological centers [2, 3]. In 2002, Polish Pediatric Leukemia and Lymphoma Study Group joined InterContinental ALL-IC-2002 group [7]. From then, for 16 years up to 2018, Polish children with ALL were treated according to ALL-IC-2002 and ALL-IC-2009 protocols.

The concept of new protocols is based on more precise risk group stratifications of patients and risk group–adapted therapy, which should lead to higher efficacy and lower toxicity of chemotherapy. This study was aimed at analysis and comparison of non-hematological toxicity of two recent pediatric ALL protocols in single center study. All patients were analyzed in two groups as defined by therapeutic protocol.

Table II. Characteristics of patients

Characteristics	Group 1	Group 2	*p*-value
Number of patients	115 (100%)	95 (100%)	
Age - Median - Range	 5.4 1.1–18.9 years	 4,4 1.2–17.6 years	0.35
Age > 6 years	57 (49.6%)	32 (33.7%)	0.03
Sex: - Female - Male	 50 (43.5%) 65 (56.5%)	 35 (36.9%) 60 (63.1%)	0.40
Initial while blood cell count >20,000/ml	44 (38.3%)	29 (30.5%)	0.31
Central nervous system involvement: - CNS1 - CNS2 - CNS3	 91 (79.1%) 20 (17.4%) 4 (3.5%)	 73 (76.8%) 15 (15.8%) 7 (7.4%)	0.85
CNS infiltrations	1 (0.9%)	1 (1%)	0.99
Organomegaly - Hepatomegaly ≥4 cm - Splenomegaly ≥4 cm - Hepatomegaly and splenomegaly ≥4 cm	 75 (65.2%) 62 (53.9%) 54 (46.9%)	 65 (68.4%) 40 (42.1%) 36 (37.9%)	 0.73 0.11 0.23
Mediastinal involvement	10 (8.7%)	2 (2.1%)	0.08
Testis involvement (male only)	1/65 (1.5%)	0/60 (0%)	0.99
Immunophenotype - Common ALL - Pre-B ALL - Pro-B ALL - Pre-T ALL - T ALL - Cortical T ALL - T-lineage, non-classified - B ALL	 87 (75.6%) 12 (10.4%) 3 (2.6%) 6 (5.2%) 4 (3.5%) 1 (0.9%) 1 (0.9%) 1 (0.9%)	 78 (82.1%) 3 (3.2%) 4 (4.2%) 5 (5.3%) 3 (3.1%) 1 (1%) 1 (1%) -	0.33
Hyperdiploidy	12 (10.4%)	23 (24.2%)	0.01
Hypodiploidy	0 (0%)	5 (5.3%)	0.04
Rearrangement BCR-ABL	5 (4.3%)	0 (0%)	0.04
Rearrangement MLL	0 (0%)	1 (1.5%)	0.99
Rearrangement TEL-AML1	24 (20.9%)	20 (21.1%)	0.99
Peripheral blood absolute blasts count at day 8 - Median - Range	 27 0–45255/ml	 70 0–141728/ml	0.27
Number of patients with ABC > 1,000 at day 8	4 (3.5%)	14 (14.7%)	0.01
Response to steroid therapy at day 8 - Prednisolone good responder (PGR) - Prednisolone poor responder (PPR)	 111 (96.5%) 4 (3.5%)	 81 (85.3%) 14 (14.7%)	0.01
Bone marrow response at day 15 - M1 (number of BM blasts <5 %) - M2 (≥5 – <25%) - M3 (≥25%)	 94 (81.7%) 16 (13.9%) 5 (4.3%)	 77 (81.0%) 17 (17.9%) 1 (1%)	0.80
MRD (flow cytometry) – day 15 of therapy - <0.1% - >0.1% – <10% - >10% No data	Not done	 39 (41.0%) 45 (47.4%) 7 (7.4%) 4 (4.2%)	Not done
Bone marrow response by day 33 - M1 - M2 - M3	 114 (99.1%) 0 1 (0.9%)	 92 (96.8%) 3 (3.2%) 0 (0.0%)	0.48
Risk group stratification - SR - IR - HR	 34 (29.6%) 66 (57.4%) 15 (13%)	 15 (15.8%) 57 (60.0%) 23 (24.2%)	0.01
CNS radiotherapy	17 (14.8%)	7 (7.4%)	0.14
Hematopoietic cell transplantation (in CR1)	14 (12.1%)	12 (12.6%)	0.99

Table III. Number of episodes of non-hematological toxicity: overall and per 1 patient

Toxicity/grade	Group 1	Group 2	p-value
Total - Grade II - Grade III - Grade IV	949 (8.25) 588 (5.11) 271 (2.36) 90 (0.78)	724 (7.62) 399 (4.20) 268 (2.82) 57 (0.60)	ns <0.001 <0.001 ns
General condition - Grade II - Grade III - Grade IV	72 (0.62) 47 (0.40) 10 (0.09) 15 (0.13)	51 (0.53) 34 (0.35) 11 (0.11) 6 (0.06)	ns
Infections - Grade II - Grade III - Grade IV	240 (2.08) 136 (1.18) 90 (0.78) 14 (0.12)	271 (2.85) 158 (1.66) 108 (1.14) 5 (0.05)	<0.001
Vomiting - Grade II - Grade III - Grade IV	96 (0.82) 89 (0.77) 4 (0.03) 3 (0.02)	23 (0.24) 22 (0.23) 1 (0.01) -	<0.001
Stomatitis - Grade II - Grade III - Grade IV	75 (0.65) 48 (0.42) 11 (0.09) 16 (0.14)	69 (0.72) 45 (0.47) 1 (0.01) 23 (0.24)	ns
Diarrhea - Grade II - Grade III - Grade IV	43 (0.37) 35 (0.30) 5 (0.04) 3 (0.03)	34 (0.35) 28 (0.29) 2 (0.02) 4 (0.04)	ns
Bilirubin concentration - Grade II - grade III - grade IV	43 (0.38) 31 (0.27) 10 (0.09) 2 (0.02)	40 (0.41) 29 (0.30) 11 (0.11) -	ns
AlAT/AspAT concentration - Grade II - Grade III - Grade IV	216 (1.88) 97 (0.84) 105 (0.91) 14 (0.12)	259 (2.72) 106 (1.11) 139 (1.46) 14 (0.15)	<0.001
Creatinine concentration - Grade II - Grade III - Grade IV	3 (0.03) 1 (0.009) 2 (0.02) -	1 (0.01) 1 (0.01) - -	ns
Proteinuria (g/L) - Grade II - Grade III - Grade IV	1 (0.009) 1 (0.009) - -	0 - - -	ns
Hematuria - Grade II - Grade III - Grade IV	3 (0.03) 2 (0.02) 1 (0.009) -	0 - - -	ns
Cardiac function - Grade II - Grade III - Grade IV	1 (0.009) - - 1 (0.009)	1 (0.01) - - 1 (0.01)	ns
Arrhythmia - Grade II - Grade III - Grade IV	2 (0.02) - - 2 (0.02)	1 (0.01) - - 1 (0.01)	ns
Central neurotoxicity - Grade II - Grade III - Grade IV	18 (0.16) 5 (0.04) 10 (0.87) 3 (0.03)	1 (0.01) - 1 (0.01) -	<0.001
Peripheral neurotoxicity - Grade II - Grade III - Grade IV	30 (0.26) 17 (0.15) 10 (0.09) 3 (0.03)	7 (0.07) 2 (0.02) 4 (0.04) 1 (0.01)	<0.001
Osteonecrosis - Grade II - Grade III - Grade IV	1 (0.009) 1 (0.009) - -	0 - - -	ns

In this study, we have shown that in both groups the most frequent toxicities included oral and gut mucositis, vomiting, diarrhea, and hepatic toxicity with transaminitis and hyperbilirubinemia. Non-hematological toxicity episodes estimated per patient were comparably often observed in both groups; however, their distribution differed between the groups. Compared to group 1, patients in group 2 had lower rate of vomiting and neurotoxicity. The decrease in vomiting reflects better level of supportive therapy performed in the department related to prophylactic use of antiemetic drugs. Such improvement in prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients is currently observed in most of the centers and reflects significant progress in the management of this complication worldwide [13, 14].

Neurotoxicity during treatment of ALL is most often presented as seizures, which might occur in up to 10% of children during intensive chemotherapy and might be caused by drug toxicity, electrolyte, or metabolic disturbances as well as infectious complications [9]. Posterior reversible encephalopathy syndrome (PRES) is another example of central neurotoxicity and is manifested as impaired vision, headaches, and seizures. It is usually caused by impaired brain circulation [15]. Most often peripheral neurotoxicity is the motor and sensory neuropathy caused by vincristine, which is always reversible [9]. In our department a significant decrease of neurotoxicity was achieved by multifactorial prophylactic strategies such as prolonged infusion of vincristine, if necessary; avoiding drug interaction with azoles; prophylaxis with anticonvulsants, if necessary; or measuring antibiotic trough concentration (e.g., vancomycin). These actions were in line with recent guidelines [16, 17].

The rate of liver toxicity including transaminitis was higher in group 2. This probably reflects the use of higher doses of chemotherapy in the second protocol. Hepatic toxicity is one of the most frequent complications during chemotherapy and expressed by elevated aminotransferases and bilirubin. Chronic hepatopathy might also occur during maintenance treatment with oral methotrexate and mercaptopurine [18]. There are no recommendations as how to prevent or alleviate chemotherapy-induced hepatotoxicity in children. Infectious complications also belong to frequent complications of antileukemic therapy [19]. In our analysis, both absolute number and their rate per 1 patient has increased over the years. It should be noted that between 2014 and 2015, antifungal prophylaxis with azoles was introduced in Poland; however, due to their interaction with vincristine it does not decrease the rate of fungal infections in children with ALL [20]. Antimicrobial prophylaxis in pediatric ALL is not recommended [21, 22], and children are more susceptible to infectious complications than adults [23].

ALL currently belongs to pediatric malignancies with superior outcome, reaching long-term survival in over 80% of the patients [7]. Nevertheless, the positive effect of therapy can be compromised by relapses and toxic complications [8, 9].

This study has some limitations. Although we analyzed toxicity during intensive chemotherapy and all patients completed this stage of treatment, the follow-up period was significantly shorter in group 2. Another issue was the learning process of the team that is responsible for care of patients. In spite of the fact that the protocol ALL-IC-2002 was developed on the basis on the BFM-ALL-95, which was used previously in the Department, still it was the new experience. In the next protocol, ALL-IC-2009, the experience of the therapeutic team in prevention of complications was much higher. This could impact lower rate of gut and neurological toxicities.

Patients treated for ALL after 2011 have currently 91% probability of overall survival [2]. The main cause of treatment failure is relapse; however, toxicity of chemotherapy is a severe issue [9, 11]. We showed that intensive treatment of ALL is burdened with frequent severe toxic and infectious complications. In conclusion, further progress in therapy of pediatric ALL will be dependent on sophisticated supportive therapy, very well experienced and knowledgeable therapeutic team.

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Authors' contributions

JS – study design. ED, JS – data analysis and interpretation. ED, JS – manuscript writing. All authors – provision of important clinical data, data check-up, final approval. ED, JS – statistical analysis. MW, JS – administrative support.

Conflict of interest

All authors declared no conflict of interest related to this study.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; and Uniform requirements for manuscripts submitted to biomedical journals.

References

[1] Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 2006;354:166–78.

[2] Demidowicz E, Pogorzala M, Lecka M, et al. Outcome of pediatric acute lymphoblastic leukemia: sixty years of progress. Anticancer Res 2019;39:5203–7.

[3] Jatczak-Gaca A, Styczynski J, Koltan A, Debski R, Pogorzala M, Wysocki M. Results of therapy in children with acute lymphoblastic leukemia in over 50 years of experience in a single center in Poland. Leuk Lymphoma 2015;56:2212–4.

[4] Pui CH, Tang JY, Yang JJ, Chen SJ, Chen Z. International collaboration to save children with acute lymphoblastic leukemia. J Glob Oncol 2019;5:1–2.

[5] Pui CH, Yang JJ, Bhakta N, Rodriguez-Galindo C. Global efforts toward the cure of childhood acute lymphoblastic leukaemia. Lancet Child Adolesc Health 2018;2:440–54.

[6] Stary J, Zimmermann M, Campbell M, et al. Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. J Clin Oncol 2014;32:174–84.

[7] Kowalczyk JR, Zawitkowska J, Lejman M, et al. Long-term treatment results of Polish pediatric and adolescent patients enrolled in the ALL IC-BFM 2002 trial. Am J Hematol 2019;94:E307–E10.

[8] Zając-Spychała O, Derwich K, Grajewska A, et al. Early complications of induction therapy in children with acute lymphoblastic leukemia treated according to the ALL IC-BFM 2002 regimen. Nowotwory. J Oncol 2009;59:448–52.

[9] Schmiegelow K, Attarbaschi A, Barzilai S, et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol 2016;17:e231–e9.

[10] Kaleta M, Zawitkowska J, Kowalczyk JR, Olcha T. Complication of intestinal perforation during chemotherapy in children with acute lymphoblastic leukemia – a report of two cases. Acta Haematol Pol 2019;50:36–9.

[11] Wolthers BO, Frandsen TL, Baruchel A, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study. Lancet Oncol 2017;18:1238–48.

[12] Biddeci G, Bosco G, Varotto E, et al. Osteonecrosis in children and adolescents with acute lymphoblastic leukemia: early diagnosis and new treatment strategies. Anticancer Res 2019;39:1259–66.

[13] Sherani F, Boston C, Mba N. Latest update on prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients. Curr Oncol Rep 2019;21:89.

[14] Paw Cho Sing E, Robinson PD, Flank J, et al. Classification of the acute emetogenicity of chemotherapy in pediatric patients: a clinical practice guideline. Pediatr Blood Cancer 2019;66:e27646.

[15] Anastasopoulou S, Eriksson MA, Heyman M, et al. Posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia: clinical characteristics, risk factors, course, and outcome of disease. Pediatr Blood Cancer 2019;66:e27594.

[16] Kandula T, Farrar MA, Cohn RJ, et al. Chemotherapy-induced peripheral neuropathy in long-term survivors of childhood cancer: clinical, neurophysiological, functional, and patient-reported outcomes. JAMA Neurol 2018;75:980–8.

[17] Sun LR, Cooper S. Neurological complications of the treatment of pediatric neoplastic disorders. Pediatr Neurol 2018;85:33–42.

[18] Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. Pediatr Blood Cancer 2018;65.

[19] O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. Blood 2014;124:1056–61.

[20] Czyzewski K, Galazka P, Fraczkiewicz J, et al. Epidemiology and outcome of invasive fungal disease in children after hematopoietic cell transplantation or treated for malignancy: Impact of national programme of antifungal prophylaxis. Mycoses 2019;62:990–8.

[21] Averbuch D, Cordonnier C, Livermore DM, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica 2013;98:1836–47.

[22] Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013;98:1826–35.

[23] Czyzewski K, Styczynski J, Giebel S, et al. Age-dependent determinants of infectious complications profile in children and adults after hematopoietic cell transplantation: lesson from the nationwide study. Ann Hematol 2019;98:2197–211.