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Central neurotoxicity as complication in course of treatment of acute lymphoblastic leukemia in children: a single center experience

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Abstract

Introduction: Neurotoxicity is a common and severe complication of the treatment of acute lymphoblastic leukemia in children, and affects 10–15% of patients. The aim of this study was to show the characteristics of this group over the course of time, the outcomes of patients, and to evaluate possible clinical risk factors for central nervous system toxicity.

Material and methods: Clinical data from patients hospitalized between 2003 and 2018 was obtained from hospital records and assessed retrospectively. Additional data was obtained to characterize the group of neurotoxic events. Statistical analysis was used to describe study group and intragroup associations, as well as event-free survival (EFS), relapse-free survival (RFS), and overall survival (OS).

The cohort comprised 224 patients (median age 5.64 years), consisting of 130 boys (58%) and 94 girls. 129 of them were treated with Protocol ALLIC BFM 2002 (57.6%), and 95 with Protocol ALLIC BFM 2009.

Results: Twenty-one patients (9.37%) developed subacute central neurotoxicity, which comprised posterior reversible encephalopathy syndrome, stroke-like syndrome and seizures, defined according to the Ponte di Legno working croup criteria. The 5-year OS and EFS of the analyzed group were 85.11% [95% confidence interval (CI): 8.32–89.82%] and 80.03% (95% CI: 74.69–85.38%) respectively. There was a statistically significant difference in EFS and RFS between neurotoxic and non-neurotoxic patients ($p = 0.00082$ and $p < 10^{-5}$ respectively), but this did not affect overall survival ($p = 0.10$). In multivariate analysis, the risks of death, adverse events and relapses were increased in patients belonging to the neurotoxicity group [hazard ratio (HR) 3.18, 95% CI: 1.26–8.06, HR 4.96, 95% CI: 2.4–10.22, HR 7.22 95% CI: 3.21–16.24, respectively).

Conclusion: The occurrence of neurotoxicity might be associated with poorer prognosis among pediatric patients with ALL.

Key words: acute lymphoblastic leukemia, children, neurotoxicity, survival

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common neoplastic disease in children, with a frequency of 35.4/1,000,000 patients [1]. Due to intensive multi-agent chemotherapy, treatment stratification directed by somatic mutations and early responses to chemotherapy, and good supportive care therapy of complications, 5-year overall survival (OS) is 90% [2]. Mortality among patients is caused more frequently by the therapy rather than by the leukemia itself. Understanding of non-infectious chemotherapy-associated acute toxicities remains limited, including the best ways to prevent and treat them. Neurotoxicity affects 10–15% of children with ALL over the course of treatment [3]. Frequently, these symptoms can endanger the lives of the patients.

Among many cytostatic drugs used in the treatment of ALL, methotrexate (MTX), cytarabine, vincristine, cyclophosphamide, iphosphamide and etoposide are the most commonly found to cause neurological complications [4]. Their interactions with many other medical substances or clinical states promote the appearance of neurotoxic symptoms.

In this paper, we present a single center experience of central subacute neurotoxic events in children with ALL treated between 2003 and 2018, show the characteristics of this group over the course of time and the outcomes of patients, and try to indicate clinical risk factors and discuss problems and controversies in the management of this clinical state, as well as to contemplate possible ways of preventing such incidents.

Material and methods

Patients and therapy

This retrospective analysis included children suffering from ALL who were treated in the Department of Pediatrics, Oncology and Hematology in the Medical University of Lodz, Poland between 2003 and 2018. All patients diagnosed with ALL and treated according to the ALLIC BFM 2002 and ALLIC BFM 2009 protocols were included in the study. Clinical data was obtained from hospital records and assessed retrospectively. We identified treatment protocol, age at onset, sex, leukemia variant, prognostic risk group [standard risk (SR), intermediate risk (IR)and high risk (HR)], central nervous system (CNS) status, steroid response, white blood cell count at diagnosis, main cytogenetics information (MLL rearrangement, *BCR/ABL* mutation), date of diagnosis, date of relapse or death, and date of last follow-up. Among all patients, a group of children who suffered from neurotoxic events was created, and additional data concerning these complications was collected — i.e. laboratory test abnormalities, the presence of other infectious or non-infectious complications of the chemotherapy in the last three weeks, any other drugs administered in the last seven days (especially MTX), symptoms of the incident, prophylaxis with theophylline, and information as to whether the neurotoxicity influenced further treatment schedule. Descriptions of the imaging diagnostic procedures were performed by an experienced radiologist and neurological events were qualified by an interdisciplinary team. This study was approved by the Bioethics Committee of the Medical University of Lodz (RNN/96/19/KE).

The analyzed central subacute neurotoxic incidents were divided into three specific groups according to the descriptions of toxic organ impairments specific for childhood acute lymphoblastic leukemia created in 2016 by the Ponte di Legno working group: i.e. seizures, methotrexate-related stroke-like syndrome (SLS), and posterior reversible encephalopathy syndrome (PRES). Although one patient did not meet the time criterion of diagnosing SLS, due to a very characteristic clinical and radiological image the child was qualified as SLS. Another case, of a girl who had typical stroke-like syndrome after liposomal cytarabine given intrathecally, was also qualified to the study as an SLS case.

Methotrexate-related stroke-like syndrome

According to the Ponte di Legno working group criteria, SLS can be diagnosed in cases of neurotoxic symptoms occurring within 21 days of intravenously (i.v.) or intrathecal (i.t.) administration of MTX with three characteristics, provided that all three are fulfilled:

1) new onset of one or more of the following: paresis or paralysis; movement disorder or bilateral weakness; aphasia or dysarthria; altered mental status including consciousness (e.g. somnolence, confusion, disorientation, and emotional lability); and/or seizures with at least one of the other symptoms;
2) characteristic, though often transient, white matter changes indicating leukoencephalopathy on magnetic resonance imaging (MRI) or a characteristic clinical course with waxing and waning symptoms, usually leading to complete (or sometimes partial) resolution within seven days;
3) no other identifiable cause [5].

Although seizures are a common feature of SLS, they can also occur without the other symptoms of SLS syndrome and may have a completely different pathophysiology. Therefore, although seizures are listed among the neurological symptoms, as an isolated symptom they do not fulfill the diagnostic criteria for SLS. The great majority of patients make a full recovery, although there have been reports of persistent neurological deficits in some cases.

To make a diagnosis of SLS, there is no need to perform imaging diagnostic procedures, although the great majority of patients have this done in order to differentiate from other pathologies e.g. stroke, hemorrhagic stroke or infiltrations of the CNS. In MRI T2-weighted scans in some patients there are visible hyperintensive white matter changes

around lateral ventricles. A few days later, an increase in intensity of those changes is usually observed, despite clinical recovery. Magnetic resonance imaging allows clinicians to distinguish between stroke-like syndrome and posterior reversible encephalopathy syndrome by opposing effects on measured apparent diffusion co-efficient (ADC) values, with SLS having reduced ADC values (due to cytotoxic edema), and PRES having increased values (due to vasogenic edema) [6].

The management of stroke-like syndrome is mainly symptomatic treatment: anti-edematous, anticonvulsant, administration of folinic acid (leucovorin) 15 mg/m^2 i.v. or higher doses depending on MTX serum concentration, as well as aminophylline — adenosine receptor antagonist [doses 2–5 mg/kg of body weight (bw)/dose i.v. or orally] [7]. Other therapeutic options include the administration of dextromethorphan 1–2 mg/kg of bw orally [8].

Posterior reversible encephalopathy syndrome

PRES is a clinical diagnosis including transient headache, confusion, seizures, and visual disturbances combined with characteristic, but transient, contrast-enhanced and diffusion-weighted imaging MRI findings. In making this diagnosis, electroencephalography (EEG) changes, as well as the presence of hypertension, may be helpful [5]. The incidence of PRES in the pediatric ALL population varies from 1.6% to 4.5% [9]. Most often it occurs during the three first months of therapy [10]. Immunosuppressive or cytotoxic drugs, autoimmune disorders, renal failure, and sepsis are all known triggers of PRES [11]. Endothelial and blood–brain barrier dysfunction are the main underlying pathophysiological mechanisms causing PRES [12]. Typical MRI findings include: patchy (and confluent) cortical (and subcortical) territory lesions in the cortex, and subcortical white matter mainly in the parietal and occipital lobes and cerebellum. Despite the word 'reversible' in its title, PRES generally has a good outcome but is not always reversible. Many sequelae, such as cerebral hemorrhage, cerebral infarction, focal gliosis, brain atrophy, and cerebral necrosis have been observed when vasogenic brain edema develops into cytotoxic brain edema [13]. Mortality in patients admitted to the intensive care unit has been assessed at 3–6%. The recurrence of PRES takes place in 4–8% of cases [14].

Older age, T-cell ALL (T-ALL), the involvement of the CNS, the presence of hypertension or hypomagnesemia, and treatment with calcineurin inhibitors or steroids are known risk factors for the occurrence of PRES [14]. Banerjee et al. [15] noted that the general outcomes of PRES patients are worse than other children with ALL (5-year OS 79.5% vs. 88.4%) and also that this group more often suffers from relapse of leukemia (45% vs. 20%). Treatment is mainly symptomatic and there is no consensus on the preferable drugs, nor on how long to maintain antiepileptic therapy [14].

Seizures

Seizures are defined by the Ponte di Legno working group as sudden, involuntary skeletal muscle contractions of cerebral or brainstem origin. They can be graded according to CTCAE: Grade 1 — brief partial seizure; Grade 2 — brief generalized seizure; Grade 3 — multiple seizures despite medical intervention; Grade 4 — life-threatening prolonged repetitive seizures; and Grade 5 — death [5]. Children with ALL treated with various protocols have had an incidence of seizures of between 1.5% and 13% [10]. Female sex, older age T-cell leukemia, CNS involvement at diagnosis and induction with dexamethasone are known to cause a higher risk of seizures [16, 17]. Epilepsy diagnosis after seizures has been reported in more than 10% of ALL survivors [17]. Long-term anticonvulsant therapy increases the systemic clearance of several antileukemic agents (e.g. teniposide, MTX), and is associated with lower efficacy of chemotherapy [18].

Statistical analysis

Study group characteristics and intragroup associations were established using Chi^2 and Mann-Whitney U-tests as well as Spearman's rank correlation coefficient and Pearson contingency coefficient. Event-free survival (EFS), relapse-free survival (RFS) and OS of the diagnosed population were evaluated using Kaplan-Meier curves and univariate Cox proportional hazards regression modelling. A log-rank test and an F Cox test was used to compare the survival of subgroups. EFS, RFS and OS were calculated from date of diagnosis to date of first event. EFS as an event was defined as time to relapse or death, and OS was defined as time to death resulting from any cause. The observation time was ceased at last follow-up if no event had occurred. p values ≤ 0.05 were considered statistically significant. All analyses have been performed using STATISTICA software version 13.1.

Results

224 children treated at the Department of Pediatrics, Oncology and Hematology at the Medical University of Lodz, Poland between 2003 and 2018 were included in this analysis. The study group comprised 130 boys (58%) and 94 girls; median age at diagnosis was 5.64 years (interquartile range: 3.29–11.65 years) and was equal in girls and boys ($p = 0.55$). More detailed characteristics of the study group are set out in Table I.

In total, 21 children experienced neurotoxicity incidents (9.37%), 13 girls (62%) and eight boys (38%). The 21 consisted of four in the ALLIC BFM 2002 protocol (19%) and 17 in the ALLIC BFM 2009 protocol (81%).

In all 21 patients, we observed 28 incidents of three different types: 16 SLS (57%), seven PRES (25%), and five seizures (18%). Seven children experienced recurrence of incident (33.3%). Most incidents took place during the

Table I. Characteristics of study group

Clinical characteristic	Median (interquartile range) or N [%]
Age at diagnosis [years]	5.64 (3.29–11.65)
Number of patients	224
Patients in Protocol 2002 Patients in Protocol 2009	129 (57.58) 95 (42.41)
Sex (female/male)	94/130
BCP-ALL T-ALL	194 (86.60%) 30 (13.40%)
WBC at diagnosis [per µL]	14,275 (4,860–48,900)
Risk group SR Risk group IR Risk group HR	44 (19.64%) 124 (55.36%) 56 (25%)
CNS1 CNS2 CNS3	180 (80.36%) 31 (13.84%) 12 (5.36%)
Poor steroid response Good steroid response	26 (11.60%) 197 (87.94%)
Death Survival	37 (16.52%) 187 (83.48%)
Event Event-free	47 (21%) 177 (79%)

BCP-ALL — B-cell progenitor acute lymphoblastic leukemia; T-ALL — T-cell acute lymphoblastic leukemia; WBC — white blood cells; SR — standard risk; IR — intermediate risk; HR — high risk; CNS — central nervous system

Table II. Detailed characteristics of study group according to neurotoxicity status

Clinical characteristic	Neurotoxicity	No neurotoxicity	*p* level
Age at diagnosis [years]*	8.48 (4.5–12.05)	5.29 (3.09–11.43)	0.05523
Number of patients	21 (9.37%)	203 (90.63%)	
Patients in Protocol 2002 Patients in Protocol 2009	4 (3%) 17 (18%)	125 (97%) 78 (82%)	0.00014
Sex (female/male)	13 (62%)/8 (38%)	81(40%)/122 (60%)	0.08675
B-ALL T-ALL	16 (17%) 5 (8%)	178 (83%) 25 (92%)	0.25605
Risk group SR Risk group IR Risk group HR	1 (2%) 14 (11%) 6 (11%)	43 (98%) 110 (89%) 50 (89%)	0.19535
CNS1 CNS2 CNS3	16 (9%) 3 (10%) 2 (17%)	164 (91%) 28 (90%) 10 (83%)	0.67009
Poor steroid response Good steroid response	2 (8%) 18 (9%)	24 (92%) 179 (91%)	0.90226
Death Survival	6 (16.22%) 15 (8.02%)	31 (83.78%) 172 (91.98%)	0.20989
Event Event free	11 (23.4%) 10 (5.65%)	36 (76.6%) 167 (94.35%)	0.00060
WBC at diagnosis [per µL]*	11,700 (5,300–23,200)	14,400 (4,860–50,000)	0.62599

*Age and white blood cells (WBC) at diagnosis are presented as median with interquartile range; B-ALL — B-cell acute lymphoblastic leukemia; T-ALL — T-cell acute lymphoblastic leukemia; SR — standard risk; IR — intermediate risk; HR — high risk; CNS — central nervous system

induction phase (42.86%), and during the treatment of relapse (25%), and more rarely during Protocol M or HR blocks (17.86%), II Protocol (10.71%) and in maintenance treatment (3.57%). Median time from beginning treatment to the occurrence of neurotoxicity was 0.52 years [interquartile range (IR): 0.14–0.97 years]. There were no significant differences between times to the occurrence of neurotoxicity and its type (p = 0.8094). 75% of incidents were associated with the presence of seizures. There was no statistically significant association between type of incident and occurrence of contractions (p = 0.18). In more than half of incidents with seizures, patients were treated with any epileptic drugs for six months. In 23% of cases, no chronic treatment was introduced and 14% finished the therapy within two months after the neurotoxicity incident.

Specific MRI presentations were revealed in 82% of incidents, whereas CT was relevant only in 18% of cases. 75% of incidents were accompanied by leucopenia and neutropenia, and in the majority of cases (53.57%) the inflammatory markers were elevated. Almost all children had been given any antibiotic in the last seven days before the incident: 25% of them had obtained meropenem, 42% piperacillin and tazobactam, and 60% other cytostatic drugs. There was no statistically significant difference between type of incident and mean time from administration of MTX (p = 0.2949). Median time was eight days (IR: 5–14 days). In 86% of patients it was intrathecal administration, while 11% got this drug via a combination of intravenous and intrathecal ways. After 50% of neurotoxic incidents, theophylline prophylaxis was introduced. Of the seven patients who suffered from a recurrence of neurotoxicity, four of them did not have prophylaxis with theophylline, two of them were given theophylline before planned lumbar puncture with administration of MTX, and there is a lack of information about one patient. Almost half of neurotoxic incidents (42.8%) caused modification of chemotherapy.

The occurrence of neurotoxicity was associated with the study protocol (p = 0.00014), although it was not a strong association (Pearson contingency correlation coefficient C = 0.2432954).

There was no significant association between occurrence of neurotoxicity and other clinical characteristics such as group of risk (p = 0.19535), sex (p = 0.08675), status of involvement of CNS (p = 0.67009), type of leukemia [B-cell ALL (B-ALL) or T-ALL] (p = 0.25605), steroid response (p = 0.90226), death (p = 0.20989), age at diagnosis (p = 0.05523), or white blood cells (WBC) at diagnosis (p = 0.62599). Detailed characteristics are set out in Table II.

The 5-year OS and EFS of the analyzed group were 85.11% [95% confidence interval (CI): 80.32–89.82%] and 80.03% (95% CI: 74.69–85.38%) respectively.

Regarding neurotoxicity occurrence, there was a statistically significant difference in EFS (p = 0.00082) (Figure 1A), but not in OS (p = 0.10135), (Figure 1B). The difference in relapse-free survival between groups of neurotoxicity and no-neurotoxicity was statistically significant (p <10^{-5}) (Figure 1C).

5-year OS in the group of children affected by this complication was 73.14% (95% CI: 54.34–91.65%) while 5-year OS in the group without neurotoxicity was 86.64% (95% CI: 81.79–91.35%). 5-year EFS, in turn, was found to be 50.41% (95% CI: 29.41–71.19%) in the neurotoxicity group, and 83.26% (95% CI: 77.91–88.38%) in the group without neurotoxicity. 5-year RFS in the neurotoxicity group was 50.63% (95% CI: 28.54–72.92%), but in the group without neurotoxicity it was 90.39% (95% CI: 86.27–94.57%).

In a model where risk factors of an adverse event were neurotoxicity and protocol, 5-year OS in the group of children affected by neurotoxicity was 51.96% (95% CI: 22.6–84.26%) in the 2002 protocol and 79.67% (95% CI: 63.51–95.43%) in the 2009 protocol, whereas in the no-neurotoxicity group it was 82.13% (95% CI: 75.51–88.67%) in 2002 and 93.06% (95% CI: 88.09–98.07%) in 2009.

5-year EFS in the group of children with neurotoxicity was 31.58% (95% CI: 5.1–57.29%) in the 2002 protocol and 57.75% (95% CI: 37.48–78.41%) in the 2009 protocol, and in the no-neurotoxicity group it was 79.04% (95% CI: 72.24–85.92%) in the 2002 protocol and 89.62% (95% CI: 83.64–95.54%) in the 2009 version. 5-year RFS for the no-neurotoxicity group was 89.66% (95% CI: 84.41–94.85%) in the ALLIC BFM 2002 protocol and 91.51% (95% CI: 86.07–97%) in the ALLIC BFM 2009 protocol, and for neurotoxicity was 45.91% (95% CI: 15.17–75.57%) in ALLIC BFM 2002 and 52.4% (95% CI: 29.66–75.35%) in ALLIC BFM 2009.

The risk of death in patients belonging to the neurotoxicity group more than trebled (HR 3.18, 95% CI: 1.26–8.06, p <0.05), the risk of an adverse event was increased by almost five times (HR 4.96, 95% CI: 2.4–10.22, p <0.05), and the risk of relapse was increased by more than seven times (HR 7.22 95% CI: 3.21–16.24, p <0.05). The ALLIC BFM 2002 protocol in this model was also a relevant risk factor of a worse outcome compared to ALLIC BFM 2009, as set out in Table III.

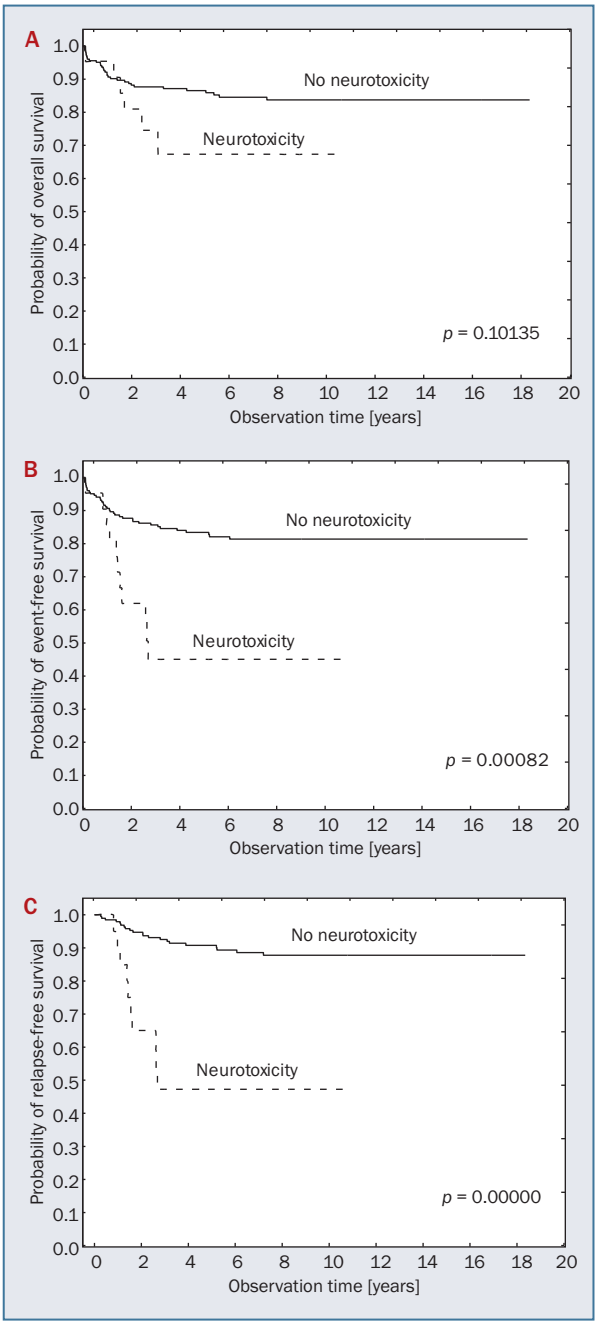

Figure 1. Survival analysis according to neurotoxicity status: **A.** Probability of overall survival; **B.** Probability of event-free survival; **C.** Probability of relapse-free survival

Because we noted that the great majority of neurotoxicity incidents and adverse events occurred to the patients in the intermediate and high risk group, and because it is widely known that they have a poorer prognosis, we checked whether there was an association between the occurrence of neurotoxicity and a higher risk group than standard. There was no statistical significance (p = 0.12989) due to the limited number of patients in the standard risk group. Differences between the neurotoxic and the no-neurotoxic

Table III. Multivariate analysis of probability survival using Cox regression modelling

Survival	Risk factor	HR	95% CI	*p* level
OS	Risk group	3.57	2.04–6.24	0.000008
	Neurotoxicity	3.18	1.26–8.06	0.14309
	ALLIC BFM 2002 protocol	0.87	0.77–0.97	0.012962
EFS	Risk group	3.45	2.1–5.69	0.000001
	Neurotoxicity	4.96	2.4–10.22	0.000014
	ALLIC BFM 2002 protocol	0.9	0.82–0.99	0.23256
RFS	Risk group	2.72	1.5–4.95	0.001032
	Neurotoxicity	7.22	3.21–16.24	0.000002
	ALLIC BFM 2002 protocol	0.97	0.87–1.08	0.607885

HR — hazard ratio; CI — confidence interval; OS — overall survival; EFS — event-free survival; RFS — relapse-free survival

group in each risk group were assessed regarding the probability of OS, EFS and RFS as shown in Figure 2, which depicts that regardless of the risk group, neurotoxicity diminished the probability of survival.

The model where risk factors of an adverse event were neurotoxicity and risk group showed that 5-year OS, 5-year EFS, and 5-year RFS were shorter in the neurotoxicity group within the risk groups of the protocols. All the results are summarized in Table IV. Hazard ratio of risk factors depicts that neurotoxicity, as well as higher protocol risk group, increased the risk of death and the occurrence of adverse events and relapses, whereas the risk was lower in the ALLIC BFM 2009 protocol. All the results are set out in Table III.

Discussion

There is a limited number of papers about neurotoxicity in the literature, and most of them are descriptions of individual cases. Few studies have been carried out on small and medium populations, and there are no clear consensus algorithms for management in this state. According to the literature, the incidence of neurotoxicity as a complication during treatment of ALL is 10–15% [3].

This is consistent with our observations (9.37%). The most common type of incident in our material was SLS (57%), although the experimental population was small (21 children, 28 incidents). We classified cases to a specific type of neurotoxicity based on the criteria of the Ponte di Legno working group 2016. However, not all the incidents met the criteria and eventually two cases were classified as SLS due to the characteristic clinical course of the incident.

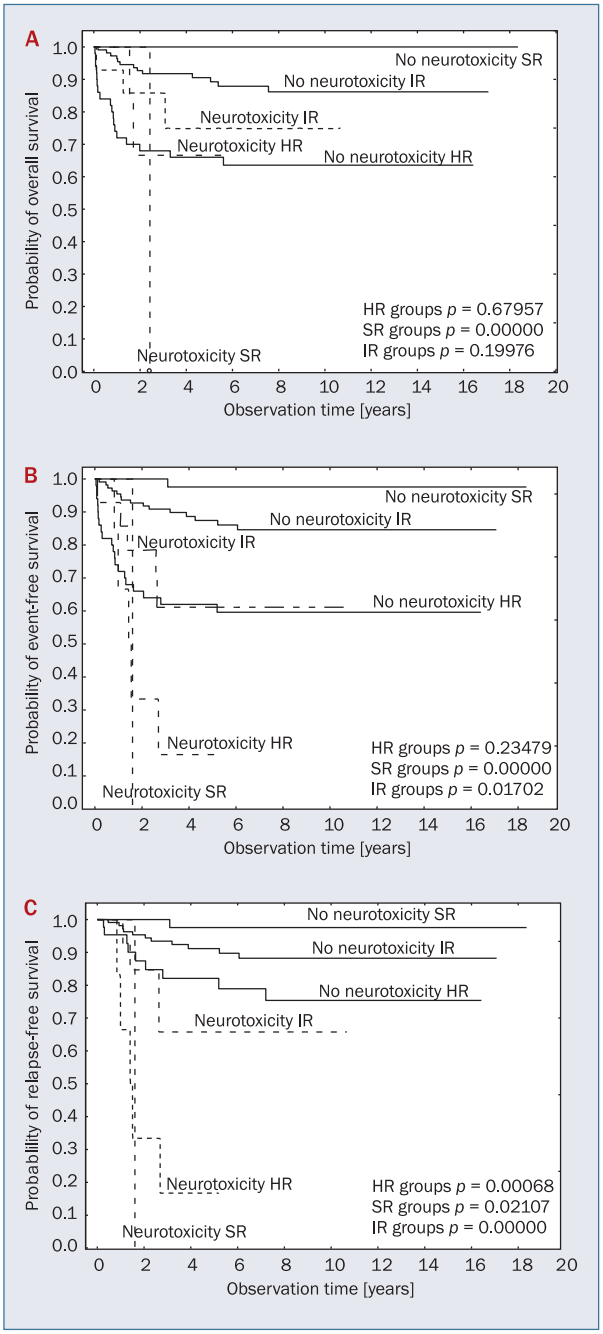

Figure 2. Survival analysis according to neurotoxicity status within risk groups of protocols: **A.** Probability of overall survival; **B.** Probability of event-free survival; **C.** Probability of relapse-free survival

The weak point of this paper is a lack of radiological verification of images — they were classified as characteristic for each type of neurotoxic event because of the description performed as the moment of diagnosis by many radiologists over the course of time. This shows the need to verify the criteria of diagnosing and differentiating between types of neurotoxicity, along with clarifying radiological features for each type of incident.

Table IV. Probability of survival according to the risk group in patients of neurotoxic and the no-neurotoxic group

Probability of survival	Risk group	Neurotoxicity	No neurotoxicity
5-year OS	SR	96.59% (95% CI: 89.87–100%)	98% (95% CI: 94.38–100%)
	IR	82.15% (95% CI: 67.36–96.68%)	89.08% (95% CI: 83.7–94.41%)
	HR	52.78% (95% CI: 23.66–81.63%)	68.88% (95% CI: 56.48–81.12%)
5-year EFS	SR	87.54% (95% CI: 70.09–100%)	96.04% (95% CI: 90.51–100%)
	IR	64.27% (95% CI: 45.07–83.62%)	87.18% (95% CI: 81.45–92.89%)
	HR	21.11% (95% CI: 0–43.72%)	61.74% (95% CI: 49.01–75.02%)
5-year RFS	SR	80.21% (95% CI: 52.42–100%)	96.44% (95% CI: 91.61–100%)
	IR	60.55% (95% CI: 38.97–82.15%)	92.13% (95% CI: 87.6–96.71%)
	HR	23.62% (95% CI: 0–50.32%)	79.06% (95% CI: 68.03–90.36%)

OS — overall survival; SR — standard risk; CI — confidence interval; IR — intermediate risk; HR — high risk; EFS — event-free survival; RFS — relapse-free survival

The majority of incidents took place in the induction phase of chemotherapy (57% in our material), irrespective of the type of incident, and that is consistent with the literature [19, 20]. Recurrence of incident for SLS is reported to be 10–56% [21], for PRES 4–8% [14], and for seizures 25% after antiseizure drug withdrawal [16].

The question arises as to how to prevent the occurrence of another incident. In our study, after nearly half of incidents (42.8%) changes in chemotherapy were introduced. In five cases, these changes depended on a reduction of the MTX dose in Protocol M, in four cases MTX i.t. was changed to cytarabine i.t. in prophylaxis of CNS, and three children had major changes in chemotherapy protocol — in the first case the parents refused the continuation of intensive treatment, the second patient had maintenance treatment introduced due to complete remission and having received long-term intensive treatment up to that moment, and the third patient after a second incident received further treatment but Protocol M was omitted.

Owing to the fact that most incidents were connected to the administration of methotrexate, there is some advice as to how to manage future administration of these drugs. According to Inaba et al. [21] in a study of six cases of neurotoxicity from a sample of 754 patients (0.8%), it seems that in most cases MTX i.t. may be re-administered without the recurrence of symptoms, although there have been no randomized trials in larger patient populations.

Most protocols state that re-exposure to MTX can be attempted (or possibly discussed with trial coordinators) once the neurotoxicity resolves [5] According to Atra et al. [22], a delay of high-dose MTH (HD-MTX) or MTX i.t. for a short time may be necessary to avoid a further neurotoxicity episode, but major changes in the chemotherapy regimen are rarely required. In a situation of recurrent episodes, in some cases in the literature MTX has been discontinued from therapy, with prophylaxis with hydrocortisone and cytarabine i.th. being maintained. This was also done in one of our patients (although we observed another neurotoxic incident after a few lumbar punctures with the administration of these drugs). The efficacy of both drugs without MTX is unknown [23].

In the literature there is grounds for the use of aminophylline as an adenosine receptor antagonist — the detection of increased adenosine in the cerebrospinal fluid of ALL children with toxic symptoms prompted Bernini et al. [7] to use an infusion of aminophylline at a dose of 2.5 mg/kg of bw, i.e. displacing adenosine from its receptors with good effect. However, there are no papers that definitively confirm the action of aminophylline, and there are no studies on the use of this drug in the prevention of methotrexate-induced neurotoxicity [24]. In our clinic, prophylactic theophylline i.v. on the day of the lumbar puncture with MTX was used, and then oral ingestion was continued for five days with the desired effect — only two of the patients had a re-incident of neurotoxicity out of the 13 who had this prophylaxis introduced.

It is an important issue in the prevention and treatment of neurotoxicity to avoid drug interactions that may also affect the overall prognosis in the disease.

MTX, the crucial drug in treatment and prophylaxis of the sanctuary sites, interacts with a range of different substances, including ciprofloxacin, non-steroidal anti-inflammatory drugs (NSAIDs), leflunomide, probenecid, penicillin, tetracyclines, chloramphenicol, cytarabine, cyclophosphamide, proton pump inhibitors, nitric oxide, theophylline, mercaptopurine, phenytoin, sulfonamides, salicylates, furosemide, folic acid, and valproic acid [25, 26]. This is a significant problem when it comes to the treatment of convulsions. They are the most common symptom of neurotoxicity; in the course of treatment this complication affects about 10% of patients with ALL, although their pathomechanisms may be varied [3]. Antiepileptic drugs have been shown to reduce the effectiveness of chemotherapy with MTX through acting with hepatic cytochromes [26] and some of them (phenobarbital, carbamazepine) also affect the active folate transporter in another mechanism [27].

The prognosis among ALL patients treated with antiepileptic drugs is worse than in a group of peers who did not receive such treatment [18]. Therefore, a safer drug was found — levetiracetam, which did not induce hepatic enzymes, and for many neurologists became the first-choice drug for convulsions in children undergoing chemotherapy [16]. A study of 81 adults who received a total of 280 MTX cycles, and 12% (33 cycles) together with levetiracetam, did not confirm the previously described interactions between levetiracetam and MTX. Indeed, they were found not to be likely without additional risk factors for prolonged MTX elimination [28]. The question as to how long to continue and when to stop anti-epileptic treatment is difficult to answer. Bond et al. have suggested that prolonged treatment is not often required after chemotherapy [4].

In this study, we observed a statistically significant association between event-free survival defined as relapse or death, and the occurrence of neurotoxicity. Due to the fact that there was no statistically significant difference in overall survival between groups with and without neurotoxicity, we can assume that these are relapses that contribute to a statistically significant poorer prognosis in these patients. Relapse referred to 47.6% of patients with neurotoxicity and death occurred in 28.6% in our study. This is consistent with the literature [29]. It is unclear whether this is due to an intrinsic tendency for some ALL cases to become complicated based on genetic predisposition, or if the increased relapse rate comes about because of suboptimal therapy. Nearly half of the patients had some modifications of the chemotherapy scheme performed, although only in three cases were these very significant. Antiepileptic drugs have been reported to be associated with faster antileukemic drug clearance and a higher risk of relapse in ALL [18], and may have contributed as a risk factor in seven of our patients. However, none of the patients died due to the occurrence of a neurotoxicity incident, which has been reported as a rare outcome previously [30].

Although our study also describes incidents of neurotoxicity in the pediatric population, it mainly focuses on survival and event-free survival in children with ALL after a neurotoxic event, in a way that is unique in the literature.

However, it has some limitations. Firstly, since this is a single center observational study, our findings should be repeated in another larger independent cohort. And the retrospective character of our study obviously limited the obtaining of some data.

Conclusions

The occurrence of neurotoxicity is associated with a poorer prognosis due to relapse and, possibly, treatment modifications. Further investigations aimed at better understanding the mechanism and predictors of subacute central neurotoxicity, as well as establishing clear classifications and guidelines of treatment, are required in order to improve treatment outcomes in pediatric ALL.

Authors' contributions

JK — conceptualization, formal analysis, writing draft manuscript; JT — providing clinical data, reviewing draft manuscript; JW — providing clinical data, reviewing draft manuscript; IDK — providing clinical data, reviewing draft manuscript; WM — conceptualization, formal analysis, reviewing and supervision of study.

Conflict of interest

The authors declare no conflict of interest.

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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.

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