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ORIGINAL ARTICLE PEDIATRICS

Acute complications observed during intensive chemotherapy in pediatric patients with acute lymphoblastic leukemia: Single-center experience

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ABSTRACT

OBJECTIVE: In childhood acute lymphoblastic leukemia (ALL), very promising results were obtained thanks to the developments in treatment strategies in recent years. However, acute complications during treatment continue to be the important causes of mortality and morbidity. In this study, acute complications that develop during the treatment of ALL in childhood were evaluated.

METHODS: Medical records of 47 patients treated according to (ALL Intercontinental Berlin-Frankfurt-Münster) 2009 protocol between 2016 and 2021 were evaluated retrospectively.

RESULTS: Of 47 patients, 28 (59.6%) were male and 19 (40.4%) were female. The mean age at diagnosis was 5.9±4.2 years. Forty-four patients (93.6%) were pre-B cell ALL, 3 patients (6.4%) were pre-T cell ALL. Of 47 patients, 9 (19.1%) were high risk, 32 (68.1%) were intermediate risk, and 6 (12.8%) were standard risk. Acute complications developed in 38 patients (80.8%). Among these complications, infectious complications are the most common and these were followed by gastrointestinal complications, drug-related reactions, thrombotic, neurological, and endocrine/metabolic complications, respectively.

CONCLUSION: In terms of complications that may develop, the threshold of suspicion should be kept low, and patients should be treated with the same medical team in fully equipped centers with a multidisciplinary approach. Inpatient treatment strategies should be applied especially in the early stages of treatment. The importance of inpatient treatment strategy, especially in the early stages of treatment, is emphasized.

Keywords: Acute complications; acute lymphoblastic leukemia; childhood.

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Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood and constitutes 25–30% of all malignancies under 15 years of age. Its annual incidence is 4/100,000 in the USA, and it is 1.5/100,000 in Turkiye according to the Ministry of Health data [1, 2]. By identifying risk factors determining the prognosis, and using risk-based treatment modalities, the success rate in treatment has exceeded 90% in our country as well as in developed countries [3]. Despite all these developments, ALL establishes a critical part of childhood mortality, and treatment-related complications (TRC) are among the causes of mortality. TRC can be life-threatening and cause disruptions in the treatment protocol, cancellations, or dose reductions in drugs. Disruptions in the treatment protocol may reduce the effectiveness

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of treatment and even increase the frequency of relapses. TRCs frequently include infections, bleeding or thrombosis, endocrine, metabolic, gastrointestinal complications, and drug toxicities, while rarer complications can also be observed [4]. In the development of these complications, the treatment protocols applied, the clinical and genetic factors related to the patient, and the characteristics of the disease have a critical role. TRCs are classified as "early acute complications" when they develop in the first 2 weeks from the onset of treatment, as "on-therapy complications" when they develop 2 weeks after the onset of treatment, and as "late complications" when they develop after recovery from the effect of the last dose of chemotherapy. While both disease-related and TRC may occur in the early treatment period, TRC are more common in the later stages of treatment [5].

This study aimed to determine early and on-therapy TRC due to chemotherapy of patients treated for ALL diagnosis.

MATERIALS AND METHODS

Medical records of patients diagnosed with ALL between 2016 and 2021 were retrospectively reviewed. Acute complications (early and on-therapy) during intensive chemotherapy of 47 patients with ALL were evaluated. Patients were treated and followed up according to ALL Intercontinental (IC) Berlin-Frankfurt-Münster (BFM) 2009 treatment protocol. In addition, tyrosine kinase inhibitors were added to the same protocol for patients with t (9; 22) positivity. Early and on-therapy complications developed during intensive chemotherapy were evaluated. Grade 3 and 4 toxicities according to common terminology criteria for adverse events v6.0 were included. The research was reviewed and approved by the institutional review board. (date: June 17, 2021 number: 194).

Patients

Patients aged 1–18 years treated according to the ALL IC BFM 2009 protocol were included in the study. Among these patients, those under the age of 1 year and those with Down syndrome were excluded from the study since the treatment protocols differed. Informed consent for treatment was obtained from each patient's legal representative before starting treatment in accordance with the Declaration of Helsinki.

Highlight key points

- Although success rates have exceeded 90% in patients with pediatric ALL, the developments in antileukemic drugs and supportive treatment methods, and risk-based treatment approaches, treatment-related complications remain a significant cause of morbidity and mortality.
- Patient monitoring should be performed considering that some complications may be seen more frequently.
- Individualized treatment options can be applied by determining patient-specific risk factors to reduce the incidence of treatment side effects.

Diagnosis

ALL was diagnosed by detecting the presence of ≥25% lymphoblast on the Wright-stained smears of bone marrow morphologically. In addition, flow cytometric immunophenotyping of bone marrow aspiration or peripheral blood samples was performed for subtype analysis. Karyotype cytogenetic assessment was performed, and translocations t (12:21), t (4:11) and t (9:22) were identified with fluorescence *in situ* hybridization and polymerase chain reaction.

Risk Stratification

Patients were classified as standard-risk (SR), intermediate-risk (IR), and high-risk (HR) according to the risk classification established by the BFM group as shown in Table 1.

Central Nervous System (CNS) Involvement

CNS involvement was defined as ≥5 cells/mL counted in cerebrospinal fluid (CSF), and lymphoblasts were determined unequivocally on cytospin. In the presence of traumatic lumbar puncture, if the leukocyte count was more than 5 cells/mL of CSF and erythrocyte-to-leukocyte ratio in cytocentrifuge preparation was equal or <100/1 with blast predominance, CNS involvement was determined. If the leukocyte count was more than 5 cells/mL of CSF and the erythrocyte-to-leukocyte ratio in cytocentrifuge preparation was more than 100/1, although CNS involvement was not considered, two additional intrathecal methotrexate doses were administered. Intracerebral infiltrations observed on cranial computed tomography or magnetic resonance imaging findings were also considered as CNS involvement.

Treatment

All the patients were classified as standard-, intermediate-, or HR groups according to the risk classification system of the protocol.

Table 1. Risk classification

Characteristics	Standard-risk (all criteria must be met)	Intermediate-risk	High-risk (at least one criterion must be met)
Age at diagnosis	>1 year and/or <6 years	<1 year and/or ≥6 years	
Leukocyte count at diagnosis	<20.000/uL	>20.000/uL	
Response to steroid at day 8	<1000 blasts/uL	<1000 blasts/uL	>1000 blasts/uL
MRD in bone marrow on day 15 (%)	<0.1	<10	>10
Bone marrow on day 15	M1 (<5% blasts by morphology) or M2 (5–25% blasts by morphology)	M1 or M2	M3
Bone marrow on day 33	M1 (<5% blasts by morphology)	M1	M2 or M3
Molecular biology	Negative for t(9;22) (BCR/ABL) or t(4;11) (MLL/AF4)	Negative for t(9;22) (BCR/ABL) or t(4;11) (MLL/AF4)	Positive for t(9;22) (BCR/ABL) or t(4:11) (MLL/AF4) or hypodiploidy ≤45 chromosomes

MRD: Minimal residual disease.

The treatment was started with protocol 1'A in the standard risk B cell precursor (SR-Bcp) patient group while with protocol 1A with extra two doses of daunorubicine in patients other than SR-Bcp ALL. Protocol 1B was administered to all patients after completing protocol 1A and 1'A. After protocol 1B was completed, protocol mM was applied to the SR patient group and protocol M to the IR group as a consolidation phase. In the HR group, HR1, HR2, and HR3 blocks were administered once as consolidation treatment for stem cell transplantation candidates, whereas twice for patients without stem cell transplantation indication. Protocol 2 was performed for all patients except stem cell transplantation candidates as reinduction treatment after completing the consolidation phase. After the protocol 2 treatment was completed, the maintenance treatment, which would be administered until the end of the 2nd year from the date of diagnosis, was started. The ALL IC BFM 2009 protocol details are summarized in Tables 2–4.

Statistical Analysis

The data were analyzed using the statistical package for social sciences (SPSS) for Windows, version 25.0 (IBM SPSS Inc., Armonk, NY). Descriptive statistical methods (mean, standard deviation, and frequency) were used while evaluating the study data. It was calculated in the 95% confidence interval when evaluating the study.

RESULTS

The clinical and laboratory findings of the patients are summarized in Table 5.

The most common type of complication observed in our study was infections. Infectious complications occurred in 32 of 47 patients (68%). Febrile neutropenia was the most common infection-related complication observed in 28 patients (87.5%), followed by urinary tract infection (n=5, 15.6%), catheter-related bloodstream infection (n=4, 12.5%), and lower respiratory tract infection (n=4, 12.5%), respectively. Thirty-one of the patients with infectious complications experienced fever at least once. Forty-five episodes of febrile neutropenia developed during the follow-up. 14 (31.1%) of these attacks occurred in the consolidation phase (HR Blocks), 13 (28.8%) in early intensification, 9 (20%) in reinduction, 7 (15.5%) in induction, and 2 (4.4%) in consolidation (protocol M) phases. Of the patients who developed infectious complications, 23 (48.9%) were in the HRG, 19 (40.4%) were in the IRG, and 5 (10.6%) were in the SRG.

Gastrointestinal complications including diarrhea, severe mucositis, and toxic hepatitis were observed in 17 patients (36.1%). Toxic hepatitis was observed in 10 patients (58.8%) in our study. Five (50%) of these developed during Protocol M, 3 (30%) during protocol 2 and 2 (20%) in protocol 1A. Of the 15-grade III-IV mucositis attacks developed in nine patients, 9 (60%) were observed during HR block treatments, 3 (20%) during protocol 2, 1 (6.6%) during protocol 1A, 1 (6.6%) dur-

Table 2. Induction (protocol I'A and protocol I A) and early intensification (protocol 1B)

Treatment	Dose	Administration time
Induction (protocol I'A and protocol I A)		
Prednisolone PO/IV	60 mg/m²/d	Days 1–28[a]
Vincristine IV	1.5 mg/m²/d (2 mg max)	Days 8, 15, 22, 29
Daunorubicin IV	30 mg/m²/d	Days 8, 15 (Protocol IA')- in SR BCP-ALL Days 8, 15, 22, 29 (Protocol IA) in SR-Tcp, IR and HR ALL
E. coli L-asparaginase IV[b]	5.000 U/m²/d	Days 12, 15, 18, 21, 24, 27, 30, 33
Methotrexate IT[c]	Dose age-adapted: <1 year: 6 mg ≥1 <2: 8 mg ≥2 <3: 10 mg ≥3: 12 mg	Days 1, 12, 33
Early intensification (protocol 1B)		
Cyclophosphamide IV	1.000 mg/m²/d	Days 36, 64
Uromitexan IV	400 mg/m²/dose	at 0, +4, and +8 h from the start of the CPM infusion.
6-Mercaptopurine PO	60 mg/m²/d	Days 36–63 (=28 days),
Cytarabine IV	75 mg/m²/d	in 4 blocks, over 4 days each, days 38–41; 45–48; 52–55; 59–62

IV: Intravenous; IT: Intrathecal; PO: Oral; Max: Maximum; SR-Tcp: Standard risk T cell precursor; CPM: Cyclophosphamide; a: Reduced by half dose every 3 days and discontinued in 9 days in total; b: In case of a hypersensitivity reaction to the *E. coli* L-asparaginase (*E. coli* ASP) formulation that would prevent reuse of the drug, either pegylated *E. coli* asparaginase (PEG-ASP) (2,500 U/m² max 3,750 U, i.v., 2 weeks apart, one dose of PEG-ASP substitutes four doses of the unmodified *E. coli* ASP.) or *Erwinia chrysanthemi* ASP (10,000 U/m² /d every other day IM on days 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34. Every seven doses of *Erwinia chrysanthemi* ASP substitute four doses of native *E. coli* ASP) could be used. The number of administration of both drugs may vary depending on when the adverse event occurs; c: In the event of CNS involvement initially, or if there is suspicion in this respect and if blasts are determined on a cytospin preparation of the first CSF which is not contaminated with the blood yet with a cell count ≤5/µL, and in the event of a traumatic LP with blasts on the cytospin preparation, and finally, when the first LP is traumatic in a patient with hyperleukocytosis >50,000/µL, additional MTX IT is given on days 18 and 27.

ing 1B, and 1 (6.6%) during protocol M. Diarrhea developed in 1 patient (5.8%). All patients for whom mucositis was observed were IR and HRG patients. Diarrhea occurred only in one SRG patient at the beginning of induction therapy. No infectious microorganism was determined for the etiology in this patient, and there was no previous history of diarrhea.

Twelve patients experienced drug-related reactions (25.5%), and all were associated with asparaginase derivatives. In addition, 5 (41.6%) of the L-asparaginase-related reactions occurred in the reinduction phase, 4 (33.3%) in the consolidation phase, and 3 (25%) in the induction phase. Both reactions developed with Peg-asparaginase were in the consolidation phase.

Thrombotic complications occurred in 4 patients (8.5%) and all of them developed in the early intensification period. One of these was cerebral sinovenous thrombosis (CSVT), which could be fatal, one was superior vena cava thrombosis, and two were superficial vein thrombosis.

Neurological complications presented as convulsions and vocal cord paralysis in 2 patients, both occurred during induction. In the treatment of the patient who had vocal cord paralysis, the use of vincristine was stopped for a while, and vitamin B6 was initiated. After the patient's hoarseness regressed and paralysis disappeared, the patient continued to receive vincristine treatments. However, the patient who had hyponatremic convulsions was not administered vincristine again during the leukemia treatment since the convulsions and hyponatremia were resistant despite appropriate treatment. Therefore, the patient had to be followed up in the intensive care unit for a long time.

Endocrine and metabolic complications were experienced in 3 of our patients. There was hyperglycemia in 2 of our patients (4.2%), and both were older than 10 years of age. One of the patients was in the induction phase of the treatment, and the other was in the HR block phase, and the patients had used corticosteroids and L-asparaginase during these two periods of treatment. The patients were started on insulin therapy. As stated in the

Table 3. Consolidation for SRG/IRG (protocol mM, protocol M) and HRG

Treatment	Dose	Administration time
Consolidation for SRG/IRG (protocol mM, protocol M)		
6-Mercaptopurine PO	25 mg/m^2/d	Days 1–56
Methotrexate IV[a]	2.000 mg/m^2/d	Four times with an interval of 14 days Days 8, 22, 36, 50.
Methotrexate IV[b]	5.000 mg/m^2/d	Four times with an interval of 14 days Days 8, 22, 36, 50.
Leucovorin Ca IV	15 mg/m2/dose	at 42 h, 48 h, 54 h after the start of MTX infusion.
Consolidation for HRG		
Block HR-1		
Dexamethasone PO/IV in 3 divided doses	20 mg/m^2/d	Days 1–5
Vincristine IV	1.5 mg/m^2 (2 mg max)	Days 1, 6
High-dose methotrexate IV	5.000 mg/m^2/d	Day 1
Leucovorin Ca IV	15 mg/m^2/dose	at: +42 h, +48 h+54 h after the start of MTX.
Cyclophosphamide IV	200 mg/m^2/d	Days 2–4
MESNA IV	70 mg/m^2/dose	at: 0 h, +4 h+8 h from the start of the CPM infusion
Cytarabine IV	2000 mg/m^2/dose 2 doses with an interval of 12 h	Day 5
E. coli L-asparaginase IV[a]	25.000 U/m^2	Day 6
Intrathecal methotrexate/ cytarabine/prednisone (or dexametasone)	Age-adjusted dose Below	Day 1
Block HR-2		
Dexamethasone PO/IV in 3 divided doses	20 mg/m^2/d	Days 1–5
High-dose methotrexate IV	5,000 mg/m^2/d	Day 1
Leucovorin Ca IV	15 mg/m^2/dose	at: +42 h, +48 h+54 h after the start of HD MTX.
E. coli L-asparaginase IV[a]	25,000 U/m^2	Day 6
Vincristine IV	1.5 mg/m^2 (2 mg max)	Days 1, 6
Ifosfamide IV	800 mg/m^2/dose 5 doses	Days 2–4
MESNA IV	300 mg/m^2/dose	Every 4 h, at 0 h, +4 h, +8 h as of the start of the IFO infusion
Daunorubicin, PI	30 mg/m^2	Day 5
Intrathecal methotrexate/ cytarabine/prednisone (or dexamethasone)	Age-adjusted dose Below	CNS-negative patients: on day 1 only CNS-positive patients: days 1 and 5
Block HR-3		
Dexamethasone PO/IV in 3 divided doses	20 mg/m^2/d	Days 1–5
E. coli L-asparaginase IV[c]	25,000 U/m^2	Day 6
Cytarabine IV	2,000 mg/m^2/dose Four doses with an interval of 12 h	Days 1, 2
Etoposide IV	100 mg/m^2/dose	Days 3–5

Table 3 (cont). Consolidation for SRG/IRG (protocol mM, protocol M) and HRG

Treatment	Dose	Administration time
	Five doses with an interval of 12 h	
Intrathecal methotrexate/ cytarabine/prednisone (or dexamethasone)	Age-adjusted dose Below	Day 5
Consolidation for HRG		
Block HR-1		
Dexamethasone PO/IV in 3 divided doses	20 mg/m^2/d	Days 1–5
Vincristine IV	1.5 mg/m^2 (2 mg max)	Days 1, 6
High-dose methotrexate IV	5.000 mg/m^2/d	Day 1
Leucovorin Ca IV	15 mg/m^2/dose	at: +42 h, +48 h+54 h after the start of MTX.
Cyclophosphamide IV	200 mg/m^2/d	Days 2–4
MESNA IV	70 mg/m^2/dose	at: 0 h, +4 h+8 h from the start of the CPM infusion
Cytarabine IV	2000 mg/m^2/dose 2 doses with an interval of 12 h	Day 5
E. coli L-asparaginase IV[a]	25.000 U/m^2	Day 6
Intrathecal methotrexate/ cytarabine/prednisone (or dexametasone)	Age-adjusted dose Below	Day 1
Block HR-2		
Dexamethasone PO/IV in 3 divided doses	20 mg/m^2/d	Days 1–5
High-dose methotrexate IV	5,000 mg/m^2/d	Day 1
Leucovorin Ca IV	15 mg/m^2/dose	at: +42 h, +48 h+54 h after the start of HD MTX.
E. coli L-asparaginase IV[a]	25,000 U/m^2	Day 6
Vincristine IV	1.5 mg/m^2 (2 mg max)	Days 1, 6
Ifosfamide IV	800 mg/m^2/dose 5 doses	Days 2–4
MESNA IV	300 mg/m^2/dose	Every 4 h, at 0 h, +4 h, +8 h as of the start of the IFO infusion
Daunorubicin, PI	30 mg/m^2	Day 5
Intrathecal methotrexate/ cytarabine/prednisone (or dexamethasone)	Age-adjusted dose Below	CNS-negative patients: on day 1 only CNS-positive patients: days 1 and 5
Block HR-3		
Dexamethasone PO/IV in 3 divided doses	20 mg/m^2/d	Days 1–5
E. coli L-asparaginase IV[c]	25,000 U/m^2	Day 6
Cytarabine IV	2,000 mg/m^2/dose Four doses with an interval of 12 h	Days 1, 2
Etoposide IV	100 mg/m^2/dose Five doses with an interval of 12 h	Days 3–5
Intrathecal methotrexate/cytarabine/ prednisone (or dexamethasone)	Age-adjusted dose below	Day 5

Table 3 (cont). Consolidation for SRG/IRG (protocol mM, protocol M) and HRG

Age-adjusted doses for intrathecal therapy in Blocks HR-1, HR-2, HR-3				
Age (year)	MTX (mg)	ARA-C (mg)	Prednisone/Dexametazone (mg)	0.9% NaCl (mL)
<1	6	16	4/1	1.5
≥1 <2	8	20	6/2	2.0
≥2 <3	10	26	8/3	2.5
≥3	12	30	10/4	3.0

IV: Intravenous; IT: Intrathecal; PO: Oral; CPM: Cyclophosphamide; ARA-C: Cytarabine; MTX: Methotrexate; a: Consolidation Therapy for SR BCP ALL patients; b: Consolidation therapy for SR and IR T-ALL/IR BCP-ALL patients; c: In the presence of a severe allergic reaction to the native *E. coli* ASP preparation, the use of the pegylated *E. coli* ASP formulation (given at 2,500 U/m^2, max 3,750 U, IV on day 6 only) or *Erwinia chrysanthemi* ASP (10,000 U/m^2/d, IM, on an alternate day: 6, 8, 10) is advised.

Table 4. Reinduction (protocol 2)

Treatment	Dose	Administration time
Reinduction (protocol 2)		
Dexamethasone PO/IV	10 mg/m^2/d, in 3 single doses	Days 1 – 21a
Vincristine IV	1.5 mg/m^2/d (2 mg max)	Days 8, 15, 22, 29.
Doxorubicin IV	30 mg/m^2/d	Days 8, 15, 22, 29.
E. coli L-asparaginase[b]	10,000 U/m^2/d	Days 8, 11, 15, 18.
Cyclophosphamide IV	1,000 mg/m^2/d	Day 36
MESNA IV	400 mg/m^2	at: 0, +4 and +8 h from the start of the CPM infusion.
6-Thioguanine PO (mg/m^2/d)	60	Days 36–49 (=14 days)
Cytarabine IV	75 mg/m^2/d	in 2 blocks, on days 38–41 & 45–48.
Intrathecal methotrexate	Dose age-adapted: <1 year: 6 mg ≥1<2: 8 mg ≥2<3: 10 mg ≥3: 12 mg	on the same day as the first dose of ARA-C in block 1 (day 38) & block 2 (day 45) In case of initial CNS involvement on days 1 and 18 of Protocol II.

IV: Intravenous; IT: Intrathecal; PO: Oral; CPM: Cyclophosphamide; a: Starting from the 22nd day, the dose is reduced to half every 3 days, and it is discontinued in a total of 9 days. b: In case of a hypersensitivity reaction to the *E. coli* ASP formulation that will prevent reuse of the drug either pegylated *E. coli* asparaginase (2,500 U/m^2 max 3,750 U, i.v, 2 weeks apart, one dose of PEG-ASP substitutes four doses of the unmodified *E. coli* ASP.) or *Erwinia chrysanthemi* ASP (10,000 U/m^2/d every other day IM on day 8,10,12,14,16,18,20 every seven doses of Erwinia chrysanthemi ASP substitute four doses of native *E. coli* ASP) can be used. The number of administration of both drugs may vary depending on when the adverse event occurs.

protocol, with the reduction of corticosteroid treatments and termination of L asparaginase use, blood glucose returned to normal levels.

The patient who experienced hyperglycemia during induction developed hypertriglyceridemia during Protocol M.

Other complications developed were psychiatric (n=1), nephrological (n=1), and vision-related complications (n=1). A total of 9 patients (19.1%) (8 IRG, one SRG) experienced no complications. All complications are listed in Table 6.

DISCUSSION

Mortality in pediatric ALL has decreased significantly through risk-based treatment modalities such as increasing the intensity of treatment in HR patients and decreasing

Table 5. Patients characteristics

Characteristics	% (n= 47)
Age (y)	
Mean	5.9±4.2
Gender	
Male/female	59.6/40.4
White blood cell (median/mean)/μL	
<20,000 μ/L	57.4
>20,000 μ/L	42.6
Initial CNS involvement	
Present	2.1
Absent	97.8
Initial mediastinal mass	
Present	2.1
Absent	97.8
Testicular involvement	
Present	2.1
Absent	97.8
Immunophenotype	
Precursor B cell	93.6
Precursor T cell	6.4
Prednisone response	
Good	93.6
Poor	6.4
Risk group	
SR	12.8
IR	68.1
HR	19.1
Chromosomal anomaly	
Absent	59.5
Hyperdiploidy	19.1
t(12;21)	14.8
t(9;22)	4.2
t(4;11)	2.1

CNS: Central nervous system.

Table 6. Complications and number of episodes during treatment

Complication	Episodes, n
Infectious	
Febrile neutropenia	45
Urinary tract infection	5
Catheter-related bloodstream infection	4
Lower respiratory tract infection	4
Herpes labialis	4
Varicella	3
Bloodstream infection	2
Cytomegalovirus	2
Preseptal cellulitis	1
Typhlitis	1
Endocarditis	1
Gastrointestinal	
Mucositis	15
Toxic hepatitis	10
Diarrhea	1
Drug-related reactions	
L-asparaginase	12
Peg-asparaginase	2
Thrombotic	
Superficial vein thrombosis	2
Intracranial thrombosis	1
Vena cava superior thrombosis	1
Neurologic	
Convulsion	1
Vocal cord paralysis	1
Endocrine/metabolic	
Hyperglycemia	2
Hypertriglyceridemia	1
Nephrologic	
Acute kidney failure	1
Psychiatric	
Depression	1
Vision-related	
Glaucoma	1

in low-risk patients, and advances in supportive treatment methods. By the individualized treatments, 5-year event-free survival and overall survival rates have increased to >80% and >90%, respectively. The leading causes of early treatment failure depend on the disease itself and TRC.

Infectious complications are still the most important cause of morbidity and mortality in patients diagnosed with ALL [6]. Patients with hematological malignancies have an increased risk of infection due to both the effect of the disease on the immune system and the immunotoxic effects of chemotherapy. Infection-related mortality has been reported to be 2–4% [7]. In addition, studies have shown that chemotherapy intensity, neutropenia, Down syndrome, and female gender are associated with increased infection-related mortality [8, 9].

Consistent with the literature, complications were observed in the intensive phases of treatment and often in HR patient groups. None of the patients died due to infection. The lack of mortality was attributed to the fact that there was no resistant microorganism or fungal in-

fection; majority of the patients were hospitalized when the fever was first observed, and antibiotic therapy was initiated promptly. Besides, the removal of the catheters promptly within the indications in patients who were found to have culture-positivity in the catheter blood through close follow-up also contributed.

The most common oral complication during ALL treatment was mucositis. Mucositis has been reported at a rate of 2–52% in patients treated for ALL in previous studies [10]. Our study revealed that severe oral mucositis developed in 9 (52.9%) patients, which prevented oral feeding. Among the risk factors, low body weight, impaired kidney function, low neutrophil count, and regimens containing high-dose methotrexate and cytarabine have been associated with more frequent development of oral mucositis [11–13]. Diarrhea observed in one SRG patient at the beginning of induction therapy stopped dramatically after intravenous prednisolone treatment was initiated. There is no report in the literature about oral prednisolone treatment causing diarrhea, and studies regarding the subject are needed.

Hepatotoxicity is common treatment-related toxicity that develops during pediatric leukemia treatments. For example, Canbolat Ayhan et al. [14] reported that 15.6% of patients treated for ALL acquired toxic hepatitis. It is not always possible to determine the factor causing toxic hepatitis in patients receiving multi-agent chemotherapy since several agents have the potential for hepatotoxicity [15].

Drug-related reactions may occur during acute leukemia treatment, and asparaginase is often the responsible agent. According to the protocol we perform on our patients, *Escherichia coli* asparaginase is administered, and in case of reaction, the treatment is changed to Peg-asparaginase or *Erwinia* asparaginase. The rate of clinical hypersensitivity reactions in the literature varies. Clinical hypersensitivity to native *E. coli* asparaginase has been reported at rates as high as 75% in ALL patients but generally ranges between 10% and 30%. Clinical hypersensitivity reactions appear to be less common with Peg-asparaginase and have been reported at rates of 3–24% in clinical studies [16–18]. In a meta-analysis conducted by Dai et al., [19] pegylated asparaginase has been shown to have lower hypersensitivity and liver injury rates than *E. coli* L-Asparaginase, associated with shorter hospital stays and reduced economic burden. Drug-related hypersensitivity reaction was observed in 12 patients in our study. All 12 patients (25.5%) had the L-asparaginase-related reaction, while an additional reaction to peg-asparaginase developed in two. In a study evaluating risk factors for asparaginase infusion-related reactions, being an HRG patient was shown to be a risk factor [20]. In our study, similar to the literature, 6 (50%) of the patients who developed a reaction were in the HRG, 5 (41.6%) were in the IRG, and 1 (8.3%) was in the SRG. The risk of antibody formation increases when patients are repeatedly exposed to asparaginase, so consolidation and reinduction are the treatment phases where hypersensitivity reactions occur with the highest incidence [21]. Decreased antibody levels have been associated with asparaginase administrations during treatment without prolonged intervals. Therefore, hypersensitivity reactions are most common in the first few doses at which asparaginase is re-administered after treatment interruption [22–24].

In the meta-analysis of Caruso et al., [18] which included 17 prospective studies, the occurrence rate of thrombotic complications in childhood ALL was found to be 5.2%. The pathophysiology of these complications includes leukemia itself, drugs used in the treatment (L-asparaginase and steroids), catheter use, and a possible prothrombotic hereditary predisposition of the patient. Although both arterial and venous thromboses have been reported, venous thrombosis is more common. CNS is the most frequently affected area in thrombotic events in pediatric patients with ALL. In the PARKAA study, which included asymptomatic cases, it was reported that the upper venous system was affected [25].

Antileukemic drugs that frequently cause thrombotic complications include steroids, L-asparaginase [26]. CSVT is one of the highly risky areas of involvement, as it has a severe mortality rate of 8–13%. Clinical suspicion, early imaging, and early anticoagulant treatment are life-saving approaches [27]. Intracranial hemorrhage was detected in one patient in whom cranial MRI was performed due to convulsions. The bleeding was suspected to be secondary to CVST. Anticoagulant treatment was initiated as soon as possible because this bleeding was mainly secondary to CSVT. Anticoagulant therapy was given until the start of maintenance therapy. After staying in the intensive care unit for a long time, the patient received maintenance therapy for gait disturbance developing in the lower extremities, which has gradually improved.

The rate of neurological complications during childhood ALL has been reported as 3–18.4% [28].

These complications may be due to the disease itself, treatment modality, or infections. The most common neurological complications have been reported

as stroke, posterior reversible encephalopathy, and peripheral neuropathy [29]. The study of Baytan et al. [28] reported that most of the cases were determined in the induction phase of the treatment. Neurological complications developed in 2 (4.2%) of the patients in our study. One of them was hyponatremic convulsion due to a syndrome of inappropriate antidiuretic hormone secretion (SIAD), and the others were vocal cord paralysis. Both complications occurred after vincristine. Vincristine is known to have a toxic effect on the central and peripheral nervous systems, despite its low penetration into the CNS through the blood-brain barrier [30]. Patient- and treatment-related risk factors have been identified in vincristine-related neurotoxicity. Being in the young age group due to immaturation of the nervous system, frequent application intervals, and short infusion time are among the risk factors [31, 32]. Both complications observed in our study occurred during the induction phase of the treatment, and the patients were under the age of 3 years.

Transient hyperglycemia frequently occurs during childhood ALL treatment. Early diagnosis and treatment are vital in preventing diabetic ketoacidosis and hyperosmolar nonketotic coma. The prevalence of hyperglycemia during ALL treatment in children has been reported to be 10–20% and is frequently seen in patients older than 10 years of age [33]. Hyperglycemia may occur due to a cause such as obesity, or it may also develop when L asparaginase causes dysfunction in pancreatic beta cells and corticosteroids to cause insulin resistance. It is often observed in the induction phase of treatment where these two drugs are combined [34–37]. The prevalence of hypertriglyceridemia in children with ALL has been reported to be 8–16%. Here, when corticosteroids and asparaginase used in the treatment are administered together, the rapid formation but insufficient removal of triglyceride-rich lipoproteins is held responsible [38]. Triglyceride levels returned to normal with the modifications applied to the diet of the patient and the use of omega-3 fatty acids.

There were also other less common adverse effects among the patients included in the study.

One of our patients had depression symptoms during protocol 2 that were not determined before diagnosis and during the earlier stages of treatment. In another patient, glaucoma was observed during protocol 1A. Both conditions were attributed to corticosteroid use. Although systemic corticosteroids have a vital place in leukemia treatment, they have a wide variety of adverse effect profiles, and one of them is psychiatric side effects, including depression, anxiety, and aggression. In a study by McGrath and Pitcher, regarding this well-known side effect, it was emphasized that the burnout of the patients and their relatives, especially during the consolidation and reinduction stages of the treatment, was added to the steroid-related side effects in the patient, and that they were able to cope with their situation more difficult [39].

Glaucoma is the second largest cause of blindness globally after cataracts and one of the most common causes of irreversible blindness [40]. In the studies, the importance of periodic examination was emphasized, especially in patients requiring long-term and high-dose corticosteroid use [41].

Another complication in our patients was methotrexate-induced renal toxicity during protocol M. The patient who experienced toxicity was in the IRG with normal renal function and methotrexate was administered at a dose of 5 g/m^2 for the 1st time. Most patients with normal renal function can be safely treated with methotrexate with intensive hydration, urine alkalization, and leucovorin rescue. Despite these preventive measures, acute and delayed toxicities remain to be a problem [42]. The study of Cheng et al. [43] stated that advanced age, higher dose of methotrexate per body surface area, low pre-treatment serum protein level, and receiving the first course of methotrexate treatment were risk factors for the development of methotrexate-induced acute kidney injury.

Conclusion

During ALL treatment, various complications may develop due to the disease or due to treatment. ALL should be treated in fully equipped multidisciplinary cancer treatment centers. The health-care team should be alert for signs and symptoms of complications. Families should also be educated about sign and symptoms of complications and so that they should urgently come to the hospital.

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