ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Acute Organ Toxicity, Biochemical and Metabolic Changes in Pediatric Oncology Patients

Çocuk Onkoloji Hastalarında Akut Organ Toksisiteleri, Biyokimyasal ve Metabolik Değişikliklerin Değerlendirilmesi

Hasan Türkmen* (0000-0001-5501-6905), Metin Demirkaya (0000-0001-6547-1872), Betül Sevinir*** (0000-0002-3232-7652)**

*Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Turkey

**Biruni University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Oncology, İstanbul, Turkey

***Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Oncology, Bursa, Turkey

Abstract

Introduction: Organ toxicity is common in childhood cancers and can cause delays in chemotherapy and worsening of prognosis. In this study, we aimed to evaluate organ toxicities, biochemical and metabolic abnormalities associated with the tumor and/or chemotherapy in the acute phase of treatment in children with cancer.

Materials and Methods: The data of 305 patients with lymphoma and solid tumors who received chemotherapy between 01.01.2010 and 31.12.2015 in a tertiary healthcare facility were retrospectively evaluated. The effects of age, gender, cancer stage, chemotherapy group, surgery and radiotherapy on organ toxicity in the first 30 days of treatment were analyzed.

Results: The mean age of the patients at admission was 97 months, and the male/female ratio was 1.5. The most common diagnoses were lymphomas (27.6%), CNS and spinal canal tumors (12.5%) and neuroblastoma (11.8%). Chemotherapy was applied to all the patients, surgery to 61.3% (n=187), and radiotherapy to 13.1% (n=40). Organ toxicity was detected in 59% (n=180) of the patients. The use of alkylating agents, antimetabolites, plant products, and no surgery were risk factors for hepatotoxicity ($p<0.05$). The only risk factor for nephrotoxicity was antimetabolite drug use ($p<0.05$). The most common electrolyte disorder was hyponatremia, observed in 56.7% (n=173) of the patients. Two patients died during the study period, which were not due to organ toxicity, metabolic disease, or electrolyte disturbance.

Conclusion: The rate of organ toxicity as well as biochemical, electrolyte, and metabolic abnormalities were found to be high. These high rates were thought to be related to the excessive tumor burden and organ involvement and the intensity of the combined chemotherapies applied. No associated mortality was observed despite these high rates. Early detection of these pathologies, close follow-up and immediate treatment with the multidisciplinary approach to treatment were described as the reason for the absence of mortality.

Öz

Giriş: Çocukluk çağı kanserlerinde organ toksisiteleri yüksek oranda görülmekte olup, kemoterapinin aksamasına ve prognozun giderek kötüleşmesine yol açabilirler. Bu çalışmada; kanserli çocuklarda tedavinin akut döneminde tümör ve/veya kemoterapi ile ilişkili görülen organ toksisiteleri, biyokimyasal ve metabolik anormalliklerin değerlendirilmesi amaçlanmıştır.

Keywords
Childhood cancers, chemotherapy, hepatotoxicity, nephrotoxicity, electrolyte imbalance

Anahtar kelimeler
Çocukluk çağı kanserleri, kemoterapi, hepatotoksisite, nefrotoksisite, elektrolit dengesizliği

Received/Geliş Tarihi : 09.12.2021
Accepted/Kabul Tarihi : 14.12.2022

DOI:10.4274/jcp.2022.02170

Address for Correspondence/Yazışma Adresi: Hasan Türkmen MD, Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Turkey
Phone: +90 224 295 04 54
E-mail: hasanturkmen28@gmail.com

Gereç ve Yöntem: Üçüncü basamak bir sağlık kuruluşunda 01.01.2010-31.12.2015 tarihleri arasında kemoterapi alan 305 lenfoma ve solid tümörlü hastanın verileri retrospektif olarak değerlendirildi. Yaş, cinsiyet, kanser evresi, kemoterapi grubu, cerrahi ve radyoterapinin, tedavinin ilk 30 gün içindeki organ toksisitesi üzerine etkileri analiz edildi.
Bulgular: Hastaların başvurudaki yaş ortalaması 97 ay, erkek/kız oranı 1,5 idi. En sık görülen tanılar sırasıyla lenfomalar (%27,6), SSS ve spinal kanal tümörleri (%12,5) ve nöroblastomdu (%11,8). Hastaların tümüne kemoterapi, %61,3'üne (n=187) cerrahi, %13,1'ine (n=40) radyoterapi uygulandı. Hastaların %59'unda (n=180) organ toksisitesi saptandı. Alkilleyici ajan, antimetabolit ve bitki kökenli ilaç kullanımı ve cerrahi uygulanmaması hepatotoksisite için risk faktörleriydi (p<0,05). Nefrotoksisite için tek risk faktörü antimetabolit ilaç kullanımıydı. En sık görülen elektrolit bozukluğu, hastaların %56,7'sinde (n=173) görülen hiponatremiydi. Çalışma döneminde organ toksisitesi, metabolik bozukluk ya da elektrolit dengesizliği ile ilişkisiz olarak 2 hasta kaybedildi.
Sonuç: Organ toksisitesi, biyokimyasal, elektrolit ve metabolik anormalliklerin oranının oldukça yüksek olduğu saptandı. Bu oranların yüksekliğinin tümör yükünün ve organ tutulumunun fazlalığı ve uygulanan kombine kemoterapilerin yoğunluğu ile ilişkili olduğu düşünüldü. Bu oranların yüksek olmasına rağmen, ilişkili mortalite gözlenmedi. Bu patolojilerin erken saptanması, yakın takibi ve buna yönelik tedavilerin multidisipliner yaklaşımla hemen uygulanması mortalite gözlenmeme nedeni olarak açıklandı.

Introduction

Antineoplastic drugs are the main components of cancer treatment. While they can prevent the proliferation of cancer cells and destroy them, they can also cause organ toxicity by affecting the liver, kidney, heart, respiratory system, nervous system as well as rapidly growing cells such as bone marrow, mucosa, and hair cells (1,2). Also organ toxicity can be seen due to disease involvement or additional treatments. Although the severity and frequency of the toxicity of chemotherapy drugs differ, failure to control the side effects may lead to a reduction or termination of the treatment dose or the patients abandoning the treatment. In this study, organ toxicities, biochemical and metabolic abnormalities associated with tumor and/or chemotherapy were evaluated in the acute treatment phase of children with cancer.

Materials and Methods

Patients aged 0-18 years with lymphoma and solid tumors who received chemotherapy at a tertiary healthcare facility, between 01.01.2010 and 31.12.2015 were included in this study. Patients with benign tumors, those who received only radiotherapy and/or surgery but did not receive chemotherapy, those who had a history of organ toxicity, chronic kidney or liver disease, those whose chemotherapy was started in another hospital and those with a history of an additional chronic disease (diabetes insipidus, etc.) were excluded. The records of 356 patients were reviewed retrospectively. Fifty-one patients who did not meet the inclusion criteria were excluded from the study, and the data of 305 patients were evaluated.

The patients' identity information, demographic data (date of birth, gender, and admission age), diagnosis, tumor location and organ involvement, tumor stage, chemotherapy protocol, drugs applied, chemotherapy start date, and surgery or radiotherapy were obtained from the hospital records.

The diagnoses were grouped as Hodgkin lymphoma, non-Hodgkin lymphomas, central nervous system (CNS) and spinal canal tumors, neuroblastoma and other peripheral nerve tumors, kidney tumors, liver tumors, bone tumors, soft tissue sarcomas and germ cell tumors, according to the International Classification of Cancer (ICCC-3). Malign epithelial neoplasms, melanomas, retinoblastoma, carcinomas, and histiocytoses were included in the "other" group, since they are seen with a low frequency in childhood. The tumor stage was classified as early (stages 1-2, non-metastatic) and advanced (stages 3-4, metastatic). Furthermore, the surgical method was divided into three groups, such as liver mass excision, nephrectomy, and mass excision in other regions. Chemotherapy drugs were classified into six groups as alkylating agents, antimetabolites, antitumor antibiotics, plant products, tyrosine kinase inhibitors, and others. Liver and kidney involvements were determined according to laboratory and imaging methods.

The patients' blood glucose, serum urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), serum electrolytes (sodium, potassium, chlorine, calcium, magnesium, phosphorus) and blood gas analysis results at admission and within one month from the start of chemotherapy were

compared with normal reference ranges for age, and they were classified as normal, low, or high (3).

The liver and kidney toxicities were determined and staged according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria (4). Based on these criteria, increases in liver transaminases up to three times the upper limit for age were considered as stage 1 hepatotoxicity, those for three to five times the upper limit for age as stage 2 hepatotoxicity, those between five and 20 times the upper limit for age as stage 3 hepatotoxicity, and those over 20 times the upper limit for age as stage 4 hepatotoxicity. Moreover, acute kidney injury was evaluated according to the increase in serum creatinine. Increases in serum creatinine by 1.5 times or more than the baseline were considered significant. Additionally, increases in serum creatinine by 1.5-2 times were considered as stage 1, increases by 2-3 times as stage 2, increases by more than 3 times as stage 3, patients with dialysis as stage 4, and death occurrence owing to renal failure as stage 5.

The collected data were compared statistically according to age, gender, cancer stage, chemotherapy drug, surgery, and/or radiotherapy application.

The study protocol was approved by Uludağ University Ethics Committee (approval number: 2016-15/17, date: 09.08.2016).

Statistical Analysis

The data were analyzed using SPSS software version 23.0 (IBM Inc., Chicago, IL, USA), and the results are given as mean ± SD, number, and percentage. Shapiro-Wilk test was performed to test for data normality. Additionally, t-test was used to compare continuous variables that conformed to the normal distribution, whereas the Mann-Whitney U test was used to compare continuous variables that did not conform to the normal distribution. Differences between categorical variables were analyzed using chi-square test, and the statistical significance level was set to $p<0.05$.

Results

The mean age of the 305 patients was 97.51±6.03 months (1 day-214 months), of which 60.0% (n=183) were male. Moreover, 10.5% (n=32) of the patients were one year old and younger, 27.9% (n=85) were between one and five years old, and 61.6% (n=188) were over five years old. The most common disease group was lymphomas [Hodgkin lymphoma, 14.1% (n=43); non-Hodgkin lymphomas, 13.5% (n=41)]. The second most common disease groups were CNS and spinal canal tumors, which accounted for 12.5% (n=38). Cancer staging was done for 176 patients, and 85 patients (48.3%) were evaluated as early stage and 91 patients (51.7%) as advanced stage.

Primary kidney tumor or metastasis to the kidney was found in 14.1% (n=43) of the patients, liver tumor or metastasis to the liver in 6.9% (n=21), and primary or metastatic tumor association of the liver and kidney in 0.7% (n=2).

The most commonly used antineoplastic drugs were plant products (91.1%, n=278), antitumor antibiotics (67.9%, n=207) and alkylating agents (67.2%, n=205), respectively. The patient characteristics are described in Table 1.

Surgery was performed on 61.3% (n=187) of the patients at admission or in the first month. Undamaged organ mass excision was performed on 51.5% (n=157), nephrectomy on 9.2% (n=28), liver mass excision on 0.3% (n=1), and primary mass and liver mass excision on 0.3% (n=1).

Radiotherapy was also performed on 13.1% (n=40) of the patients before chemotherapy and/or in the first month of chemotherapy.

Organ toxicity was detected in 59% (n=180) of the patients, of which 2.6% of the patients (n=8) had only nephrotoxicity, 48.5% (n=148) had only hepatotoxicity, and 7.9% (n=24) had both hepatotoxicity and nephrotoxicity. Two (0.7%) of the patients died in the first month, one due to progressive disease and the other due to septicemia.

The hepatotoxicity and nephrotoxicity rates are given according to the stages in Table 2. Stage 1 hepatotoxicity (32.1%, n=98) was the most common, whereas stage 4 hepatotoxicity (4.3%, n=13) was the least common. Nephrotoxicity was also detected in 10.5% (n=32) of the patients, of which stage 1 was the most common (8.5%, n=26) and stage 4 (requiring dialysis) was observed in two patients (0.7%).

At least one electrolyte disorder was found in 87.5% (n=267) of the patients. The most common electrolyte abnormality was hyponatremia with a rate of 56.7% (n=173). Table 3 gives the rates of biochemical abnormalities and electrolyte disturbances.

The blood gas of 79 patients was analyzed, and 21 patients (26.6%) had metabolic acidosis, 9 patients (11.4%) had metabolic alkalosis, 13 patients (16.5%)

Table 1. Characteristics of the patients	
Age [month, mean ± SD (range)]	97.51±6.03 (0.03-214)
Gender [n, (%)]	
Male	183 (60.0)
Female	122 (40.0)
Primary disease [n, (%)]	
Hodgkin lymphoma	43 (14.1)
Non-Hodgkin lymphomas	41 (13.5)
B-cell lymphomas	32 (10.5)
T-cell lymphomas	9 (3.0)
CNS and spinal canal tumors	38 (12.5)
Neuroblastoma and other peripheral nerve tumors	36 (11.8)
Kidney tumors	28 (9.2)
Liver tumors	3 (1.0)
Bone tumors	28 (9.2)
Soft tissue sarcomas	26 (8.5)
Germ cell tumors	33 (10.8)
Other	29 (9.5)
Chemotherapy drug group [n, (%)]	
Alkylating agents	205 (67.2)
Antimetabolites	59 (19.3)
Antitumor antibiotics	207 (67.9)
Plant products	278 (91.1)
Tyrosine kinase inhibitors	1 (0.3)
Other	49 (16.1)

CNS: Central nervous system, SD: Standard deviation

Table 2. Hepatotoxicity and nephrotoxicity rates according to the stage	
Hepatotoxicity [n, (%)]	
None	133 (43.6)
Stage 1	98 (32.1)
Stage 2	24 (7.9)
Stage 3	37 (12.1)
Stage 4	13 (4.3)
Nephrotoxicity [n, (%)]	
None	273 (89.5)
Stage 1	26 (8.5)
Stage 2	0 (0.0)
Stage 3	4 (1.3)
Stage 4	2 (0.7)

had respiratory acidosis, and 25 patients (31.6%) had respiratory alkalosis.

The organ toxicity rates of the patients were compared according to gender, age, cancer stage, whether radiotherapy was applied, whether surgery was performed, and the chemotherapy groups they received.

Table 3. Prevalence of biochemical abnormalities and electrolyte imbalances	
Biochemical abnormality [n, (%)]	
Hypoglycemia	35 (18.2)
Hyperglycemia	46 (24.0)
High uric acid	59 (20.1)
Hypoalbuminemia	111 (39.5)
Hyperbilirubinemia	71 (26.6)
High ALP	23 (21.5)
High GGT	10 (38.5)
Electrolyte imbalance [n, (%)]	
Hyponatremia	173 (56.7)
Hypernatremia	16 (5.2)
Hypokalemia	91 (29.8)
Hyperkalemia	144 (47.2)
Hypochloremia	99 (32.7)
Hyperchloremia	148 (48.8)
Hypocalcemia	115 (38.5)
Hypercalcemia	16 (5.4)
Hypomagnesemia	41 (17.7)
Hypermagnesemia	76 (32.9)
Hypophosphatemia	97 (39.0)
Hyperphosphatemia	30 (12.0)

ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Since the number of patients receiving tyrosine kinase inhibitors in the first month of treatment was insufficient (n=1, 0.3%), it was excluded from the statistical analysis.

It was observed that gender, age, cancer stage, and radiotherapy intake did not make any significant difference when risk factors for hepatotoxicity and nephrotoxicity were compared. Hepatotoxicity was significantly higher in patients who did not undergo surgery (66.9%) than those who received surgery (49.7%) (Table 4).

Hepatotoxicity was significantly higher in patients who received alkylating agents (64.4%) compared to those who did not (40%), patients who received antimetabolite drugs (94.9%) compared to those who did not (47.2%), and patients who received "other" chemotherapy (84.7%) compared to those who did not (50.8%) (Table 5). There was also no significant difference in hepatotoxicity between patients who received plant products and those who did not, as well as between patients who received antitumor antibiotic drugs and those who did not. The rate of nephrotoxicity was found to be significantly higher in patients who received antimetabolite drugs (23.7%) compared to those who did not (7.3%) ($p<0.05$). There was no significant difference in the rate of nephrotoxicity between those who used alkylating agents, plant products, antitumor antibiotics and "other" group chemotherapy and those who did not.

Discussion

In this study, organ toxicity and biochemical, electrolyte, and metabolic abnormalities in the first month of chemotherapy were evaluated in childhood

Table 4. Comparison of risk factors for hepatotoxicity and nephrotoxicity

	Hepatotoxicity [n, (%)]		p value	Nephrotoxicity [n, (%)]		p value	Total [n, (%)]
	Yes	No		Yes	No		
Male Female	109 (59.60) 63 (51.60)	74 (40.40) 59 (48.40)	0.17	24 (13.10) 8 (6.60)	159 (86.90) 114 (93.40)	0.06	183 (100.00) 122 (100.00)
≤5 age >5 age	63 (53.80) 109 (58.00)	54 (46.20) 79 (42.00)	0.47	13 (11.10) 19 (10.10)	104 (88.90) 169 (89.90)	0.78	117 (100.00) 188 (100.00)
Early stage Late stage	49 (57.60) 59 (64.80)	36 (42.40) 32 (35.20)	0.32	8 (9.40) 9 (9.90)	77 (90.60) 82 (90.10)	0.91	85 (100.00) 91 (100.00)
RT (-) RT (+)	155 (58.50) 17 (42.50)	110 (41.50) 23 (57.50)	0.05	28 (10.60) 4 (10.00)	237 (89.40) 36 (90.00)	0.91	265 (100.00) 40 (100.00)
Surgery (-) Surgery (+)	79 (66.90) 93 (49.70)	39 (33.10) 94 (50.30)	0.003*	17 (14.40) 15 (8.00)	101 (85.60) 172 (92.00)	0.07	118 (100.00) 187 (100.00)

*p<0.05, RT (-): Those who do not receive radiotherapy, RT (+): Those who receive radiotherapy, Surgery (-): Those who do not undergo surgery, Surgery (+): Those who undergo surgery

Table 5. Comparison of hepatotoxicity and nephrotoxicity rates by chemotherapy group

	Hepatotoxicity [n, (%)]		p value	Nephrotoxicity [n, (%)]		p value	Total [n, (%)]
	Yes	No		Yes	No		
Alkylating (-) Alkylating (+)	40 (40.00) 132 (64.40)	60 (60.00) 73 (36.60)	<0.001*	7 (7.00) 25 (12.20)	93 (93.00) 180 (87.80)	0.16	100 (100.00) 205 (100.00)
A.M. (-) A.M. (+)	116 (47.20) 56 (94.90)	130 (52.80) 3 (5.10)	<0.001*	18 (7.30) 14 (23.70)	228 (92.70) 45 (76.30)	<0.001*	246 (100.00) 59 (100.00)
P.P. (-) P.P. (+)	20 (74.10) 152 (54.70)	7 (25.90) 126 (45.30)	0.05	5 (18.50) 27 (9.70)	22 (81.50) 251 (90.30)	0.15	27 (100.00) 278 (100.00)
A.A (-) A.A (+)	56 (57.10) 116 (56.00)	42 (42.90) 91 (44.00)	0.86	13 (13.30) 19 (9.20)	85 (86.70) 188 (90.80)	0.27	98 (100.00) 207 (100.00)
Other (-) Other (+)	130 (50.80) 42 (84.70)	126 (49.20) 7 (14.30)	<0.001*	23 (9.00) 9 (18.40)	233 (91.00) 40 (81.60)	0.05	256 (100.00) 49 (100.00)

*p<0.05, A.M.: Antimetabolites, P.P.: Plant-products, A.A.: Antitumor antibiotics

lymphoma and solid tumors, and these abnormalities were found to be at a high rate. No associated mortality was observed despite these high rates.

Hepatotoxicity can manifest itself in a wide spectrum from mild elevation of transaminase levels to severe hepatic insufficiency and coma. In our study, the rate of hepatotoxicity was significantly higher in patients who did not undergo surgery as well as those who received alkalinizing agents, antimetabolite drugs, and "other" chemotherapy. Meanwhile, age group, gender, cancer stage, and radiotherapy did not affect the hepatotoxicity rate.

The hepatotoxicity rate (64.4%) was significantly higher in patients who received alkylating drugs compared to those who did not. Mcdonald et al. (5) reported hepatotoxicity in 16% of 147 patients with adult leukemia and lymphoma who received cyclophosphamide, and De Vita et al. (6) reported hepatotoxicity in 15% of adult patients with lymphoma and solid tumors who received carmustine. In our study, hepatotoxicity was significantly higher in patients who received antimetabolite group chemotherapy (94.9%) compared to those who did not. In the study by Weber et al. (7) with 40 children with leukemia who received high-dose methotrexate, liver transaminase levels were found to be high in 33% in the first cycle and 100% in the fifth cycle. It was observed that the liver transaminase levels returned to normal within two weeks after the drug was discontinued. Oğuz et al. (8) detected an elevation of transaminase levels between stages 1 and 3 in 10 pediatric patients with Burkitt's lymphoma who received methotrexate, and the transaminase levels returned to normal within 2-11 days in nine of the 10 patients. The hepatotoxicity rate performed with methotrexate, a drug with known liver toxicity, in the study was similar to the hepatotoxicity of the antimetabolite group in our study.

In the present study, hepatotoxicity in patients who received antitumor antibiotics was not significantly different from those who did not. Damodar et al. (9) found hepatotoxicity in 30.4% of 46 adult breast cancer patients who received doxorubicin. Green et al. (10) found hepatotoxicity in 13% of 37 patients with Wilms' tumor who received dactinomycin and vincristine treatment. Bisogno et al. (11) found hepatotoxicity in 8% of 511 Wilms' tumor patients who received dactinomycin and vincristine.

Moreover, 54.7% of the patients in our study who took plant-based antineoplastic drugs had hepatotoxicity, and no significant difference was found compared to those who did not. Chen et al. (12) reported hepatotoxicity in 8.9% of 45 patients who received paclitaxel and lobaplatin due to esophageal squamous cell carcinoma.

The hepatotoxicity rate was significantly higher in patients who received "other" chemotherapy (L-asparaginase, corticosteroids) compared to those who did not. Oettgen et al. (13) reported increased transaminase levels in 46% of the children and 63% of the adults in their study of 131 children and 143 adults diagnosed with leukemia, lymphoma, and solid tumors who received chemotherapy combined with L-asparaginase. During the first two months of follow-up of 57 patients diagnosed with acute lymphoblastic leukemia (ALL) who received induction chemotherapy, Christ et al. (14) reported stages 3-4 hepatotoxicity in 60% of patients receiving PEG-asparaginase and 33% of patients receiving L-asparaginase. Wolff et al. (15) found that when dexamethasone was administered with high-dose methotrexate in patients with brain tumors, methotrexate toxicity increased. In our study, unlike other studies, drugs were examined in groups rather than individually due to combined chemotherapy application. The fact that our hepatotoxicity rate was higher than that of other studies was thought to be due to the examination of drugs in groups.

Cancer and chemotherapy-related nephrotoxicity can be seen as obstructive uropathy, prerenal azotemia due to hypovolemia, renal parenchymal damage due to chemotherapy or organ involvement, or mass effect. The rate of nephrotoxicity was 10.5% in our study, and it did not significantly differ according to age group, gender, cancer stage, surgery, and radiotherapy. Nephrotoxicity rate was higher in patients taking antimetabolite drugs than those who did not.

When the nephrotoxicity rates were examined according to the chemotherapy group, there was no significant difference in nephrotoxicity detected in 12.2% of patients who used alkylating agents compared to those who did not. Kiu et al. (16) reported nephrotoxicity in two patients (9.5%) after two cycles of chemotherapy in their study with 21 adults with malignant glioma who received carmustine and cisplatin after surgery and radiotherapy. Kobayashi et

al. (17) reported 13.7% nephrotoxicity in 4-7 days after the first course in 219 patients who received cisplatin. In this study, there was no difference between male and female patients in terms of toxicity rate. The rate of nephrotoxicity in our study was similar to the rate in this study, and there was no gender difference in terms of nephrotoxicity. Khalil et al. (18) reported acute renal failure in 31.8% of 365 adults diagnosed with lymphoma who underwent cyclophosphamide, vincristine, prednisolone (CVP), adriamycin, bleomycin, vinblastine, dacarbazine (ABVD), and cyclophosphamide, daunorubicin, oncovin, prednisone (CHOP) chemotherapy protocols, and this rate is higher than that in our study. In our study, nephrotoxicity was more frequent in patients using antimetabolite drugs (23.7%) compared to those using other chemotherapy agents. Moreover, hematuria was significantly more common in patients who took antimetabolite drugs (49.1%) compared to those who did not. Kaya et al. (19) found nephrotoxicity in 13% of 42 children with ALL who received high-dose methotrexate treatment, Widemann et al. (20) found nephrotoxicity in 1.8% of 3,887 patients diagnosed with osteosarcoma who received high-dose methotrexate, and reported that 4.4% of patients who developed kidney damage died.

In this study, nephrotoxicity was observed in 9.2% of patients who received antitumor antibiotics, and there was no significant difference in nephrotoxicity or urinalysis results between these patients and those who did not. There are very few studies in the literature that showed that antitumor drugs cause nephrotoxicity. Meanwhile, animal studies show that anthracyclines can cause kidney failure through free radical damage. Since antitumor antibiotics were used in combination with other chemotherapy drugs in our study, we could not determine whether they caused only nephrotoxicity.

Nephrotoxicity was also observed in 9.7% of patients who took plant products, and there was no significant difference in the rates of nephrotoxicity or urinalysis results for these patients compared to those who did not. Agaliotis et al. (21) reported nephrotoxicity in 48% of 131 patients who received ifosfamide, carboplatin, etoposide (ICE) protocol. Yahanda et al. (22) reported nephrotoxicity in 12% of 72 patients who took etoposide and cyclosporine, and the rate of nephrotoxicity in their study is similar to that of our study. However, the relationship between plant products and nephrotoxicity could not be determined due to combined chemotherapy use in this study.

Nephrotoxicity was also observed in 18.4% of patients who received "other" chemotherapy, and there was no significant difference in the rates of nephrotoxicity or urinalysis results for these patients compared to those who did not. Haskell et al. (23) reported acute renal failure in two (3.6%) of 55 patients with leukemia and solid tumors who received L-asparaginase in the third week of treatment. Meanwhile, there are few studies in the literature that reported all-trans retinoic acid (ATRA) nephrotoxicity. Yaralı et al. (24) reported acute glomerulonephritis in a patient who received ATRA for acute promyelocytic leukemia. Elsayed et al. (25) reported that ATRA increased the nephrotoxic effect of cisplatin in mouse experiments.

At least one electrolyte imbalance was found in 87.5% (n=267) of patients participating in the study. The most common electrolyte imbalance was hyponatremia (56.7%). Alsirafy et al. (26) reported at least one electrolyte disorder in 78.7% of 750 patients diagnosed with cancer. In this study, the most common electrolyte imbalance was hyponatremia (59%), and the rates coincide with our study. Milionis et al. (27) reported at least one electrolyte and acid-base imbalance in 62% of 66 patients with leukemia, and hypopotassemia was the most common electrolyte disorder (63%).

Blood gas analysis was performed for only 79 patients in our study, and 31.6% of the patients had respiratory alkalosis, 26.6% had metabolic acidosis, 16.5% had respiratory acidosis, and 11.4% had metabolic alkalosis. Milionis et al. (27) found that 9% of 66 patients with acute leukemia had metabolic acidosis, 6% had metabolic alkalosis, 4.5% had respiratory alkalosis, and 3% had respiratory acidosis. In the study, patients who took corticosteroids, diuretics, aminoglycoside, amphotericin, and supplementary drugs (such as potassium, magnesium, and phosphorus) that may affect their acid-base balance were excluded from the study; hence, the acid-base imbalance rates were lower than those in our study.

The strengths of our study are large number of patients involved and the diversity of diagnosis, organ toxicity, electrolyte disorders, acid-base imbalances and the simultaneous evaluation of biochemical abnormalities. However, one of its limitations is

that it is a retrospective study. Moreover, the lack of evaluation of other conditions (sepsis, antibiotic use, diuretic use, etc.) affecting fluid-electrolyte balance and organ functions are the weaknesses of this study.

Conclusion

In this study, in which the first month of treatment of pediatric oncology patients receiving chemotherapy was evaluated, the rate of organ toxicity, biochemical, electrolyte, and metabolic abnormalities were found to be high. These high rates were thought to be related to the excessive tumor burden and organ involvement and the intensity of the combined chemotherapies applied. No associated mortality was observed despite these high rates. The early detection of these pathologies, their close follow-up, and the immediate application of treatment with a multidisciplinary approach were explained as the reason for not having mortality. The side effect rates can be further reduced with up-to-date and good knowledge of the tumor or chemotherapy-related toxicities by physicians treating oncology patients, with an early multidisciplinary approach and appropriate supportive treatment.

Ethics

Ethics Committee Approval: The study protocol was approved by Uludağ University Ethics Committee (approval number: 2016-15/17, date: 09.08.2016).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Creutzig U, Zimmermann M, Reinhardt D, Dworzak M, Stary J, Lehrnbecher T. Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukemia: Analysis of the multicenter clinical trials AML-BFM 93 and AML-BFM 98. J Clin Oncol 2004;22:4384-93.
2. Janeway KA, Grier HE. Sequelae of osteosarcoma medical therapy: a review of rare acute toxicities and late effects. Lancet Oncol 2010;11:670-8.
3. Stanley F.Lo. Reference intervals for laboratory tests and procedures. In: Kleigman RM, Behrman RE, Jenson HB, Stanton BP (eds). Nelson Textbook of Pediatrics. 20th edition. Philadelphia: Saunders Elsevier; 2011. p.3467-72.
4. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. (cited May 29, 2009). Available from: URL: http://evs.nci.nih.gov
5. Mcdonald GB, Slattery JT, Bouvier ME, Ren S, Batchelder AL, Kalhorn TF, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. Blood 2003;101:2043-8.
6. De Vita VT, Carbone PP, Owens AH Jr, Gold GL, Krant MJ, Edmonson J. Clinical trials with 1,3-bis(2-chloroethyl)-nitrosourea, NSC-409962. Cancer Res 1965;25:1876-81.
7. Weber BL, Tanyer G, Poplack DG, Reaman GH, Feusner JH, Miser JS, et al. Transient acute hepatotoxicity of high-dose methotrexate therapy during childhood. NCI Monogr 1987;5:207-12.
8. Oğuz A, Hasanoğlu A, Ezgü FS. Methotrexate Related Acute Hepatotoxicity. Gazi Med J 2002;13:69-72.
9. Damodar G, Smitha T, Gopinath S, Vijayakumar S, Rao Y. An evaluation of hepatotoxicity in breast cancer patients receiving injection Doxorubicin. Ann Med Health Sci Res 2014;4:74-9.
10. Green DM, Finklestein JZ, Norkool P, J.D'Angio G. Severe hepatic toxicity after treatment with single-dose dactinomycin and vincristine. A report of the national Wilms' tumor study. Cancer 1988;62:270-3.
11. Bisogno G, de Kraker J, Weirich A, Masiero L, Ludwig R, Tournade MF, et al. Veno-occlusive disease of the liver in children treated for Wilms tumor. Med Pediatr Oncol 1997;29:245-51.
12. Chen MQ, Chen C, Lu HJ, Xu BH. The efficacy and toxicities of combined lobaplatin with paclitaxel as a first-line chemotherapy for advanced esophageal squamous cell carcinoma. J Thorac Dis 2015;7:1749-55.
13. Oettgen HF, Stephenson PA, Schwartz MK, Leeper RD, Tallai L, Tan CC, et al. Toxicity of E. coli L-asparaginase in man. Cancer 1970;25:253-78.
14. Christ TN, Stock W, Knoebel RW. Incidence of asparaginase-related hepatotoxicity, pancreatitis, and thrombotic events in adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen. J Oncol Pharm Pr 2017;23:1-10.
15. Wolff JEA, Hauch H, Kühl J, Egeler RM, Jürgens H. Dexamethasone increases hepatotoxicity of MTX in children with brain tumors. Anticancer Res 1998;18:2895-9.
16. Kiu MC, Chang CN, Cheng WC, Lin TK, Wong CW, Tang SG, et al. Combination chemotherapy with carmustine and cisplatin before, during, and after radiotherapy for adult malignant gliomas. J Neurooncol 1995;25:215-20.
17. Kobayashi R, Suzuki A, Matsuura K, Yamada N, Nakano M, Deguchi T, et al. Risk analysis for cisplatin-induced nephrotoxicity during first cycle of chemotherapy. Int J Clin Exp Med 2016;9:3635-41.
18. Khalil MA, Latif H, Rehman A, Kashif WU, Awan S, Khalil Z, et al. Acute kidney injury in lymphoma: a single centre experience. Int J Nephrol 2014;2014:272961.
19. Kaya Z, Gursel T, Bakkaloglu SA, Kocak U, Atasever T, Oktar SO. Evaluation of renal function in Turkish children receiving BFM-95 therapy for acute lymphoblastic leukemia. Pediatr Hematol Oncol 2007;24:257-67.
20. Widemann BC, Balis FM, Kempf-Bielack B, Bielack S, Pratt CB, Ferrari S, et al. High-dose methotrexate-induced

nephrotoxicity in patients with osteosarcoma. Cancer 2004;100:2222-32.

21. Agaliotis DP, Ballester OF, Mattox T, Hiemenz JW, Fields KK, Zorsky PE, et al. Nephrotoxicity of high-dose ifosfamide/carboplatin/etoposide in adults undergoing autologous stem cell transplantation. Am J Med Sci 1997;314:292-8.
22. Yahanda AM, Alder KM, Fisher GA, Brophy NA, Halsey J, Hardy RI, et al. Phase I trial of etoposide with cyclosporine as a modulator of multidrug resistance. J Clin Oncol 1992;10:1624-34.
23. Haskell CM, Canellos GP, Leventhal BG, Carbone PP, Block JB, Serpick AA, et al. L-asparaginase: therapeutic and toxic effects in patients with neoplastic disease. N Engl J Med 1969;281:1028-34.
24. Yarali N, Tavil B, Kara A, Ozkasap S, Tunç B. Acute renal failure during ATRA treatment. Pediatr Hematol Oncol 2008;25:115-8.
25. Elsayed AM, Abdelghany TM, Akool el-S, Abdel-Aziz AA, Abdel-Bakky MS. All-trans retinoic acid potentiates cisplatin-induced kidney injury in rats: Impact of retinoic acid signaling pathway. Naunyn Schmiedebergs Arch Pharmacol 2016;389:327-37.
26. Alsirafy SA, Al-Shahri MZ, Hassan AA, Hidayatullah M, Ghanem HM. Pattern of electrolyte abnormalities among cancer patients referred to palliative care: A review of 750 patients. Prog Palliat Care 2007;15:182-6.
27. Milionis HJ, Bourantas CL, Siamopoulos KC, Elisaf MS. Acid-Base and Electrolyte Abnormalities in Patients With Acute Leukemia. Am J Hematol 1999;207:201-7.