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Original Article

Analysis of Nephrotoxicity and Hypokalemia during the Use of Liposomal Amphotericin B in Children with Febrile Neutropenia

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ABSTRACT

Purpose: Invasive fungal infections are an important cause of morbidity and mortality in children with febrile neutropenia. Although liposomal amphotericin B (L-AMB) is used safely due to its broad antifungal activity, it causes important side effects such as nephrotoxicity and hypokalemia.

Methods: Medical records of 45 children with hematological malignancies who were given empirical L-AMB for febrile neutropenia between November 2011 and December 2019 were reviewed retrospectively. The estimated glomerular filtration rate (eGFR), serum creatinine and potassium levels were compared before and after 7th day of L-AMB treatment.

Results: 62 febrile neutropenic attacks of 45 children were evaluated. The median age of the patients was 8.25 (3.5-13) years, and the number of attacks per patient was between 1-5. The median duration of treatment with L-AMB was 14 (range 9-21) days. Nephrotoxicity developed in 16 attacks (26%), and hypokalemia developed in 26 attacks (42%). In those who developed nephrotoxicity, eGFR was lower and creatinine level was higher after 7th day of L-AMB treatment, compared to their values before treatment. The frequency of hypokalemia was low in attacks where nephrotoxicity has been developed. High eGFR, and low creatinine level were risk factors with borderline significance from the point of development of nephrotoxicity.

Conclusion: Potassium level should be carefully monitored and appropriate replacement therapy should be administered in febrile neutropenic children with hematological malignancy receiving L-AMB therapy. Parenteral hydration before L-AMB administration does not prevent nephrotoxicity, however it positively affects the frequency of nephrotoxicity.

Introduction

Despite advances in the diagnosis and treatment, invasive fungal infection (IFI) still represents a major complication in severely immunocompromised hosts undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) for hematological malignancy [1]. Retrospective and prospective analyses show that patients receiving intense chemotherapy such as acute myeloid leukemia (AML) and HSCT, are the highest risk group for IFI [2]. However, patients with lymphoma and acute lymphoblastic leukemia (ALL) also carry high risk from the point of IFI [3]. The incidence of IFI is 41.2% in children with AML, 29.4% in children with ALL, and 28.3% in children who underwent allogeneic HSCT [4]. Liposomal amphotericin B (L-AMB) and caspofungin are first-line agents in empirical treatment [5].

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Renal dysfunction and hypokalemia are well-known side effects of L-AMB. L-AMB affects both glomerular and tubular functions. Impairment in glomerular functions reveals itself with a decrease in glomerular filtration rate and consequent increases in serum urea and creatinine concentrations. Distal tubulopathy is characterized by potassium loss, metabolic acidosis, hypomagnesemia, and loss of the ability to concentrate the urine [6].

There are few studies in the literature examining L-AMB-related nephrotoxicity and hypokalemia in immunosuppressed children. Pediatric patients with malignancies receive many chemotherapeutic and anti-infective treatments that are inevitably nephrotoxic. In addition, they tend to be hypokalemic due to loss from the gastrointestinal tract and inadequate oral intake. Thus, it is very difficult to determine the incidence of L-AMB-related nephrotoxicity and hypokalemia in these patients.

In this retrospective study, nephrotoxicity and hypokalemia on the 7th day after L-AMB treatment were analysed in children who developed febrile neutropenic attacks while under chemotherapy and received empirical L-AMB treatment with multiple anti-infective therapy.

Materials and Methods

Children with hematological malignancies who were given empirical L-AMB treatment for febrile neutropenic attack while under chemotherapy between November 2011 and December 2019, were included in the study. Data regarding age, gender, diagnosis, L-AMB dose, L-AMB treatment duration, complete blood count parameters (haemoglobin, white blood cell count, absolute neutrophil count, platelet count), C-reactive protein (CRP) and procalcitonin levels, intravenous (IV) hydration amount received during L-AMB treatment were recorded from the files of the patients. The estimated glomerular filtration rate (eGFR), serum potassium and creatinine levels were analysed before and after 7th day of L-AMB treatment.

Pediatric RIFLE (pRIFLE) criteria were used to assess nephrotoxicity [7]. The pRIFLE criteria were obtained by modifying the adult RIFLE criteria. It consists of three graded injury levels (risk, injury, failure) and two outcome measures (loss of kidney function, end stage kidney disease) based on the magnitude of the change in eGFR. A 25% reduction in eGFR was defined as 'risk', 50% reduction as 'injury', and 75% reduction as 'failure'. Since 24-hour urine collection is difficult in pediatric patients, eGFR was calculated using the Schwartz formula. Schwartz formula was calculated using the equation;

eGFR (mL/min/1.73m^2): k×(height (cm))/(serum creatinine (mg/dl))
k= 0.55 in children and adolescent girls
k= 0.70 in adolescent boys

The severity of hypokalemia was evaluated according to the common terminology criteria for adverse events (CTCAE). A serum potassium level of 3-3.5 mmol/L was classified as mild; 2.5-3 mmol/L as moderate and <2.5 mmol/L as severe hypokalemia [8]. Analyses performed in the study were as follows;

i. Clinical and laboratory characteristics of patients.
ii. eGFR, serum creatinine, potassium levels before and after 7th day of L-AMB treatment.
iii. Frequency of nephrotoxicity, frequency and severity of hypokalemia after 7th day of L-AMB treatment.
iv. eGFR, serum creatinine, potassium levels before and after 7th day of L-AMB treatment in those who developed nephrotoxicity.
v. eGFR, serum creatinine, potassium levels before L-AMB treatment and the duration of L-AMB use in patients with and without nephrotoxicity.
vi. Risk factors for nephrotoxicity.

Statistical Analysis

Data analyses were performed using SPSS 18 (IBM SPSS Corp.; Armonk, NY, USA) package programme. Values for qualitative variables were given as incidence and percentage, and for quantitative variables as mean±standard deviation (SD) or median (Q1-Q3). The conformity of quantitative variables to normal distribution was evaluated with the Shapiro Wilk test. In the analysis of data before and after L-AMB, dependent samples t test (paired t test) was used for normally distributed variables, and Wilcoxon test was used for non-normally distributed variables. In the comparison of the data of attacks with and without nephrotoxicity; the t test was used for normally distributed variables and the Mann Whitney U test was used for non-normally distributed variables. Logistic regression analysis was used to identify risk factors associated with the development of nephrotoxicity. Cases with $p<0.05$ were considered as significant.

Results

In the study, 62 febrile neutropenic attacks of 45 patients were evaluated. Eighteen (40%) of the patients were female, 27 (60%) were male, and their median age was 8.25 (3.5-13) years. The number of febrile neutropenic attacks per patient was between 1-5. Thirty-five of the patients (77%) had received chemotherapy with the diagnosis of acute lymphoblastic leukemia, 5 of them (11%) with non-Hodgkin lymphoma, 2 of them (5%) with aplastic anemia, 2 (5%) with hemophagocytic lymphohistiocytosis and 1 (2%) with neuroblastoma. Median haemoglobin level was 8.8 g/dL (7.9-9.6), leukocyte count was 700/mm^3 (377.5-1600.0), absolute neutrophil count was 100/mm^3 (0.0-412.5), platelet count was 39.000/mm^3 (22.500-69.750), CRP was 10.8 mg/ dL (5.2-19.5) and procalcitonin level was 0.5 mg/mL (0.2-3.7). Nephrotoxicity developed in 16 (26%) of the attacks. 7 attacks (11%) were evaluated in the risk group, 8 attacks (13%) in the injury group, and 1 attack (1%) in the failure group. Hypokalemia developed in 26 attacks (42%) on the 7 days after L-AMB treatment. Mild hypokalemia developed in 15 attacks (24%), moderate hypokalemia in 9 attacks (15%), and severe hypokalemia in 2 attacks (3%). Hypokalemia occurred in 7 (27%) of the attacks where nephrotoxicity developed and in 19 (73%) of the attacks where no nephrotoxicity developed. The clinical features and laboratory parameters of the patients are shown in (Table 1).

Table 1: Clinical characteristics and laboratory parameters of the patients.

	Number of patients (n/%)
Gender (Female/Male)	18 (40 %)/27 (60 %)
Acute lymphoblastic leukemia	35 (77%)
Non-Hodgkin Lymphoma	5 (11%)
Aplastic anemia	2(5%)
HLH	2 (5%)
Neuroblastoma	1(2%)
Total	45 (100%)
	Median (Q1-Q3)
Age (years)	8.25 (3.5-13)
Haemoglobin (g/dl)	8.8(7.9-9.6)
Leukocyte count (/mm^3)	700(377.5-1600)
Absolute neutrophil count (/mm^3)	100(0-412.5)
Platelet count(/mm^3)	39000 (22500-69750)
CRP (mg/dl)	10.8(5.2-19.5)
Procalcitonin (ng/ml)	0.5 (0.2-3.7)
pRIFLE criteria	**Number of febrile neutropenia attacks (n/%)**
Risk	7 (11%)
Injury	8 (13%)
Failure	1 (2%)
Total	16 (26%)
Hypokalemia	**Number of febrile neutropenia attacks (n/%)**
Mild	15 (24%)
Moderate	9 (15%)
Severe	2 (3%)
Total	26 (42%)

CRP: C-reactive protein; HLH: Hemophagocytic lymphohistiocytosis.

L-AMB treatment was started at a dose of 3 mg/kg/day in all patients and was increased to 5 mg/kg/day in 4 patients. The duration of treatment with L-AMB was 14 (range 9-21) days. All patients received different combinations of antibiotics (meropenem, cefepime, amikacin, vancomycin, teicoplanin) before and during L-AMB treatment. Parenteral hydration (0.45% NaCl) was applied to all patients before and after L-AMB treatment, because their oral intake was not sufficient due to the reasons such as abdominal pain, vomiting and oral mucositis. On the 7th day after L-AMB treatment, the amount of potassium replacement was 40 (range 20-80) mEq/L.

There was no statistical difference between eGFR and serum creatinine levels before and 7th day after L-AMB treatment ($p>0.05$ for both). The serum potassium level at 7th day after L-AMB treatment was lower than the level before L-AMB treatment ($p<0.001$) (Table 2).

Table 2: eGFR, creatinine and potassium levels before and after 7 days of L-AMB treatment in all attacks and in attacks where nephrotoxicity developed.

All attacks (n=62)			
	Before L-AMB treatment	**After 7 days of L-AMB treatment**	**P**
eGFR (ml/min/1,73m^2)	198.7 (165-263.3)	189 (148-237)	0.14
Creatinine (mg/dl)	0.32 (0.23-0.43)	0.37 (0.24-0.49)	0.074
Potassium (mmol/L)	4.04±0.61	3.64 ±0.65	<0.001
	Attacks with nephrotoxicity (n=16)		
eGFR (ml/min/1,73m^2)	308.5 (230.70-340.40)	165.5 (94.90-196.20)	<0.001
Creatinine (mg/dl)	0.23 (0.17-0.32)	0.49 (0.27-0.67)	<0.001
Potassium (mmol/L)	4.12±0.56	3.77±0.68	>0.05

eGFR: Estimated glomerular filtration rate.

In attacks developing nephrotoxicity, eGFR values on the 7th day after L-AMB treatment was lower than the values before L-AMB treatment ($p<0.001$) and creatinine levels were higher ($p<0.01$). There was no difference in terms of serum potassium levels ($p>0.05$) (Table 2). In attacks with nephrotoxicity, eGFR value was higher ($p<0.001$) and creatinine level was lower ($p<0.01$) compared to attacks without nephrotoxicity. There was no difference between the two groups in terms of serum potassium level and duration of L-AMB treatment ($p>0.05$ for both) (Table 3).

Table 3: eGFR, creatinine and potassium levels before L-AMB treatment in attacks with and without nephrotoxicity and duration of L-AMB treatment.

	Attacks with nephrotoxicity (n=16)	**Attacks without nephrotoxicity (n=46)**	**P**
eGFR (ml/min/1,73m^2)	305(263.30-337)	187(160.50-225)	<0.001
Creatinine (mg/dl)	0.25(0.17-0.30)	0.37(0.26-0.47)	<0.01
Potassium (mmol/L)	4.12±0.56	4.0±0.64	>0.05
Duration of L-AMB treatment (days)	14(10-18)	14(9-22)	>0.05

eGFR: Estimated glomerular filtration rate.

Using logistic regression analysis, it was determined that high eGFR (OR: 1.016; 95% CI: 1.007-1.026, p=0.001) and low creatinine levels (OR: 1.059; 95% CI: 0.00-0.397, p=0.019) found, were the risk factors with borderline significance for nephrotoxicity. Since almost all of our patients received L-AMB standardly at 3 mg/kg dose, the L-AMB dose was insufficient to evaluate as a risk factor.

Discussion

Our results showed that parenteral hydration before L-AMB did not protect from nephrotoxicity in febrile neutropenic children with hematological malignancy, but it had a positive effect on the frequency of nephrotoxicity, and high amounts of potassium replacement was needed to maintain potassium levels after L-AMB treatment. In addition, it was found that high eGFR and low serum creatinine were borderline significant risk factors for nephrotoxicity, and that the frequency of hypokalemia was lower in attacks developing nephrotoxicity.

In studies on L-AMB-related nephrotoxicity in pediatric patients, the frequency of nephrotoxicity has been reported as 11% and 21.2%, although there are differences in terms of L-AMB dose, patient population, and nephrotoxicity criteria [9-11]. In studies, doubling of the basal creatinine level was generally accepted as a criterion for nephrotoxicity. Dutta *et al.*, reported the incidence of nephrotoxicity as 43% in a small number of pediatric patients receiving immunosuppressive therapy according to the pRIFLE criteria [12]. The researchers explained the reason for the higher frequency of nephrotoxicity compared to other studies, with the feature of pRIFLE criteria to detect kidney damage at an earlier stage. Considering the difficulty of 24-hour urine collection in our study, we evaluated L-AMB-related nephrotoxicity in a larger cohort of immunosuppressed children using the pRIFLE criteria for the sake of practicality. In terms of nephrotoxicity, 7 patients (11%) were in the risk group, 8 patients (13%) were in the injury group, and 1 patient (2%) was in the failure group. After L-AMB treatment, serum creatinine levels of the patients in the injury and risk groups increased approximately 2-4 times compared to the values before L-AMB treatment. Therefore, when we accepted a 2-fold increase in basal creatinine values as a nephrotoxicity criteria as in other studies, our nephrotoxicity incidence corresponded to 14%. From this point of view, it is seen that the frequency of nephrotoxicity is not very high in our patients who have received multiple chemotherapy and multiple anti-infective treatment as the neutropenic fever treatment.

All reports describing pediatric AMB nephrotoxicity agree that there is a decrease in eGFR. The decrease in eGFR shows itself by increases in creatinine concentrations. When we analysed patients who developed nephrotoxicity, we found a decrease in eGFR after L-AMB treatment, when compared to before treatment L-AMB values, and an increase in creatinine levels (Table 2). Studies in both humans and animals have shown that saline administration can protect against the AMB-induced reduction in eGFR or ameliorate it [13-15]. Therefore, oral or parenteral fluid and electrolyte supplementation prior to AMB infusion has been accepted as a reasonable approach in this high-risk population [15, 16]. Parenteral hydration was administered to all of our patients before and during L-AMB treatment, because their oral intake was insufficient due to symptoms such as mucositis, anorexia and nausea. We thought that the low frequency of nephrotoxicity in our study was related to adequate hydration before L-AMB treatment.

Adult studies have reported an inverse relationship between renal function and development of nephrotoxicity in patients treated with L-AMB. Alvarez Lema *et al.* reported that L-AMB has little effect on kidney function in critically ill patients who have impairment in renal function [17]. Kato *et al.* reported a significant increase of serum creatinine level after L-AMB treatment in patients with normal renal function compared to patients with impaired renal function [18]. In our study, it was determined that eGFR before L-AMB treatment were higher in patients who developed nephrotoxicity compared to those who did not, and that high eGFR and low creatinine levels were risk factors with borderline significance.

It is believed that hypokalemia develops due to the toxic effect of AMB on the renal tubules. In animal models, the number of apoptotic tubular cells has been shown to be associated with the degree of hypokalemia and loss of kidney concentrating ability [19]. In the literature, the frequency of L-AMB-related hypokalemia has been reported as 36-58% [20-23]. In our study, the frequency of hypokalemia after L-AMB treatment was 42%. In addition, the frequency of hypokalemia in attacks that developed nephrotoxicity was lower than in attacks without nephrotoxicity. This phenomena can be explained with the results obtained by Kobayashi *et al.* [20]. In this study, it was reported that a normal eGFR is a risk factor for the development of hypokalemia after L-AMB therapy, hypokalemia is less common in low eGFR, and it has been suggested that the possible reason for this is related to the decrease of potassium excretion by low eGFR. According to the results of our study, we observed that although eGFR decreased after L-AMB in those who developed nephrotoxicity, hyperkalemia didn't develop in any of the patients, on the contrary, they tended to develop hypokalemia under potassium replacement. Therefore, we concluded that hypokalemia rather than hyperkalemia is a problem that should be coped with, in these patients. There is some evidence that hypokalemia may increase kidney damage [24, 25]. Takazano *et al.* related serum potassium levels of <3.5 mmol/L (hypokalemia) before L-AMB treatment, with the stage 2 and 3 acute kidney injury [26]. Chronic, persistent hypokalemia is associated with acute kidney injury through vacuolar degeneration of proximal and distal renal tubule cells. Therefore, they suggested that correction of

hypokalemia prior to L-AMB administration is important to reduce acute kidney injury [27].

In conclusion, even though we have included patients with similar diseases, receiving similar treatments, many variables (cumulative chemotherapeutic, combinations of anti-infective agent, and presence of infection) may have influenced the results. The decrease in eGFR and increase in serum creatinine levels after L-AMB treatment are similar with those of other studies in the literature. The difference was that eGFR was high in attacks that developed nephrotoxicity. The fact that the frequency of nephrotoxicity in our study was lower than the rates reported in the literature, may be related to the hydration before and during L-AMB administration. Although potassium replacement is applied during L-AMB therapy, hypokalemia is an important problem and the frequency of hypokalemia is lower in those who develop nephrotoxicity. The hydration status and potassium levels of pediatric patients receiving immunosuppressive therapy under L-AMB treatment should be carefully monitored. It might be a beneficial approach to support hydration before the drug therapy, in the patients for whom L-AMB treatment is planned.

Conflicts of Interest

None.

Author Contributions

Z.C.Ö., and YDK designed the study. M.B., E.T., and Y.D.K., collected, analysed, and interpreted the clinical data. H.Ö., performed the statistical analysis. Z.C.Ö, wrote the manuscript in consultation with ÖB. All the authors have read and approved the final version of the manuscript.

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Ethical Approval

This study was approved by the College of Medicine Institutional Review Board (ethical approval no:54/2020).

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