Hyperuricemia and tumor lysis syndrome in children with non-Hodgkin's lymphoma and acute lymphoblastic leukemia

Non-Hodgkin lenfoma ve akut lenfoblastik lösemili çocuklarda hiperürisemi ve tümör lizis sendromu

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Abstract

Objective: This study aimed to examine the incidence, clinical characteristics, and outcome of hyperuricemia and tumor lysis syndrome (TLS) in children with non-Hodgkin's lymphoma (NHL) and acute lymphoblastic leukemia (ALL).

Materials and Methods: This retrospective study included data from 327 patients (113 NHL and 214 ALL).

Results: Hyperuricemia occurred in 26.5% and 12.6% of the patients with NHL and ALL, respectively. The corresponding figures for TLS were 15.9% and 0.47% (p=0.001). All hyperuricemic NHL patients had advanced disease and renal involvement was present in 53%. All hyperuricemic ALL patients had a leukocyte count >50,000 mm^3 at the time of diagnosis. Among the hyperuricemic NHL and ALL patients, 96.6% and 66.6% had LDH ≥500 UI/L, respectively. Treatment consisted of hydration and allopurinol; none of the patients received urate oxidase. Among the patients that developed TLS, 26.3% had laboratory TLS, 42.1% had grade I or II TLS, and 31.6% had grade III or IV TLS. Uric acid levels returned to normal after a mean period of 3.5±2.5 and 3.05±0.8 d in NHL and ALL groups, respectively. In all, 7% of the patients with hyperuricemia required hemodialysis. None of the patients died.

Conclusion: In this series the factors associated with a high-risk for TLS were renal involvement in NHL and high leucocyte count in ALL. Management with allopurinol and hydration was effective in this group of patients with high tumor burden. *(Turk J Hematol 2011; 28: 52-9)*

Key words: Non-Hodgkin's lymphoma, leukemia, tumor lysis syndrome, hyperuricemia, children

Özet

Amaç: Çalışmanın amacı NHL ve ALL'li çocuklarda hiperürisemi ve TLS sıklığını, klinik özellikleri ve sonuçlarını tanımlamaktır.

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Yöntem ve Gereçler: Bu retrospektif çalışmada 113 NHL ve 214 ALL'li toplam 327 hastanın verileri değerlendirildi.

Bulgular: NHL olgularının %26.5'inde, ALL olgularının %12.6'sında hiperürisemi görüldü. TLS insidansı NHL ve ALL gruplarında %15.9 ve %0.47 bulundu (p=0.001). Hiperürisemi görülen NHL olgularının tümü ileri evrede olup, %53'ünde renal tutulum vardı. Tüm hiperürisemili ALL olgularında tanıda lökosit sayımı 50.000/mm³'den yüksekti. Hiperürisemik NHL grubunun %96.6'sında, ALL grubunun %66.6'sında LDH ≥500 UI/L idi. Tedavide hidrasyon ve allopürinol uygulandı, ürat oksidaz verilen hasta olmadı. TLS gelişen olguların %26.3'ünde laboratuvar TLS, %42,1'inde grade I ve grade II TLS, %31.6'sında grade III ve IV TLS saptandı. Ürik asit düzeyleri NHL ve ALL hastalarında ortalama 3.5±2.5 ve 3.05±0.8 günde normale döndü. Hiperürisemili hastaların %7'sinde hemodiyaliz gerekti. Mortalite olmadı.

Sonuç: Bu seride en yüksek TLS riski renal tutulumu olan NHL olgularında saptandı. Allopürinol ve hidrasyonun tümör yükü yüksek olan bu grupta etkili olduğu gözlendi. *(Turk J Hematol 2011; 28: 52-9)*

Anahtar kelimeler: Non-Hodgkin lenfoma, lösemi, tümör lizis sendromu, hiperürisemi, çocuklar

Introduction

Tumor lysis syndrome (TLS) is a complication of cancers that are highly sensitive to cytotoxic agents, and have a high tumor burden and proliferation rate. Acute renal injury may ensue due to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Uric acid is an important mediator of renal injury in TLS, and hyperuricemia is one the first signs of TLS [1,2]. Nonetheless, not all patients with hyperuricemia develop other signs of TLS. Although TLS may also occur in solid tumors, patients with non-Hodgkin's lymphoma (NHL) and acute leukemia represent the majority of cases [1-3].

In Turkey acute leukemias and lymphomas are the most frequent childhood cancers [4,5]. NHL and acute lymphoblastic leukemia (ALL) are frequently associated with a number of adverse metabolic consequences due to high cell turnover and a high response rate to cytotoxic agents. Most children in Turkey with NHL are diagnosed at an advanced stage [4,6]. As such, metabolic disturbances that require urgent treatment are frequently observed. Among these, hyperuricemia has recently emerged as an important complication associated with the use of newer therapeutic agents. Allopurinol, a xanthine oxidase inhibitor, has traditionally been used to treat hyperuricemia; it blocks the production of uric acid from xanthine and hypoxanthine without affecting the breakdown of already formed uric acid, and at the same time prevents new production.

Alkalinization of urine may increase the excretion of uric acid via urine [1,2]. In recent years, recombinant urate oxidase has been introduced, which is an enzyme that exists in many mammalians, but not humans. This enzyme allows urinary excretion of uric acid by converting it to allantoin, which is 5-10-fold more soluble in water than uric acid; however, urate oxidase causes hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency and is expensive. Hyperuricemia and acute TLS may lead to adverse consequences, including renal insufficiency or sudden death. TLS has been graded on the basis of laboratory and clinical features, with the Cairo and Bishop TLS classification systems being the most recent [7]. Additionally, guidelines for preventing morbidity and mortality have been issued, despite the lack of a consensus.

In Turkey the incidence of hyperuricemia in children with NHL and ALL has not been specifically addressed and, therefore, the present study aimed to determine the frequency, grade, clinical course, and outcome of hyperuricemia in children with NHL and ALL. Moreover, the efficacy of the protocol used at our hospital for the prevention and treatment of hyperuricemia and TLS was re-assessed.

Material and Methods

Patients

The medical records of children with NHL and ALL that were treated at our hospital between January 1997 and December 2007 were retrospectively evaluated. Age, gender, histopathological group, disease stage, and the presence of renal involvement, and serum lactate dehydrogenase (LDH), urea, uric acid, creatinine, calcium, phosphorus, and electrolyte levels were assessed in NHL

patients. In the patients with ALL, age, gender, leukocyte count at the time of diagnosis, risk group status, and the presence of renal involvement, and serum LDH, urea, uric acid, creatinine, calcium, phosphorus, and electrolyte levels were assessed.

Spontaneous or post-chemotherapy elevation of uric acid levels and signs of acute TLS were recorded, as were the response to the routine hyperuricemia management protocol, number of days required for normalization of uric acid levels, number of patients that required hemodialysis, and mortality data. The Local Ethical Committee of Uludağ University Medical Faculty approved this retrospective study (Approval number: 2009-11/80).

Chemotherapy protocol

The NHL BFM-95 and ALL BFM-95 protocols were used for the treatment of NHL and ALL patients, respectively.

Criteria for hyperuricemia and acute tumor lysis syndrome

Serum uric acid levels above normal were considered hyperuricemia (normal range: 2.2-7.2mg/dL). TLS was defined on the basis of Cairo and Bishop criteria [7]. Accordingly, laboratory TLS (L TLS) criteria were as follows: serum uric acid ≥8mg/ dL (476 μmol/L), serum potassium ≥6 mEqL^{-1} (6 mmol/L), serum phosphorus >6.5 mg/dL (2.1 mmol/L), and serum calcium <7 mg/dL (1.75 mmol/L), or a 25% increase from baseline in the first 3 parameters, or a 25% decrease from baseline in serum calcium. Fulfillment of at least 2 laboratory criteria from 3 d prior to cytotoxic treatment to 7 d after was diagnostic for LTLS. Clinical TLS (CTLS) was defined on the basis of renal, cardiac, and neurological changes (Table 1). Data for hyperuricemic patients were classified according to LTLS and CTLS criteria.

Routine management protocol for hyperuricemia

Routine prophylaxis and treatment were given to all the NHL and ALL patients. As such, all patients with uric acid levels at the upper limit of normal or those with a high risk of acute TLS received intravenous hydration and oral allopurinol. Hydration was given for 24 h be be fore chemotherapy and the total daily dose ranged between 2500 and 3000 mL/m^{-2}. The urine density and pH range were set at 1010 and 6.7-7, respectively. Allopurinol - 300 and 200 mg·m^{-2} ·d^{-1} p.o. - was given in 3 divided doses to the NHL and ALL patients, respectively. None of the patients received urate oxidase.

Table 1. Cairo-Bishop TLS grading system [7]

	LTLS	Creatinine	Cardiac arrhythmia	Seizure
Grade 0	-	<1.5 × ULN	None	None
Grade I	+	1.5 × ULN	Intervention not indicated	-
Grade II	+	1.5-3 × ULN	Non-urgent medical intervention	Brief, generalized seizure(s) controlled with anticonvulsants, or infrequent focal motor seizures not interfering with daily activity
Grade III	+	3-6 × ULN	Symptomatic and incomplete	Seizures in which consciousness is altered, controlled medically or poorly controlled, with breakthrough generalized control, with device seizures despite medical intervention
Grade IV	+	>6 ≈ ULN	Life threatening (e.g. arrhythmia associated with congestive heart, failure, hypotension, syncope, shock)	Seizure of any kind that is prolonged, repetitive, or difficult to control (e.g. status epilepticus, intractable epilepsy)
Grade V	+	Death	Death	Death

ULN: Upper limit of normal; LTLS: laboratory tumor lysis syndrome

Table 2. Patient characteristics

	NHL	ALL	P
Number of patients	113	214	-
Median age [years] (range)	6.5 (0.9-17.3)	5.5 (1.16-17.5)	0.8
Gender (n, male/female)	90/23	131/83	-
Stage III, IV (n, %)	110 (97.3)	-	-
High WBC* (n, %)	-	28 (13)	-
LDH† (UI/L)	895 ± 1246	372 ± 213	0.02
High LDH level** (n, %)	64 (56)	26 (12)	
Uric Acid† (mg/dL)	5.79 ± 4.13	5.81 ± 2.37	0.2
Urea† (mg/dL),	30.5 ± 35.8	26.6 ± 12.5	0.3
Creatinine† (mg/dL)	0.74 ± 0.9	0.53 ± 0.11	0.11
Renal involvement (n, %)	32 (28.2)	-	
Hyperuricemia (n, %)	30 (26.5)	27 (12.6)	0.05
ATLS (n, %)	18 (15.9)	1 (0.47)	0.001

ATLS: Acute tumor lysis syndrome, *High white blood cell count (WBC) ≥50,000 mm^{-3}, **LDH ≥500 IU/L , †Normal laboratory ranges: UA: 2.2-7.2 mg/dL; Cr: 0.6-1.3 mg/dL; urea: 10-50 mg/dL; LDH: 125-243 IU/L (mean ± SD)

Statistical method

Age, LDH concentration, biochemical parameters, and leukocyte counts are presented as mean±standard deviation (SD). Gender, hyperuricemia, hyperleukocytosis, and the frequency of TLS are presented as percentages. The NHL and ALL groups were compared using the t-test and chi-square test to determine the significance of the differences between means, and between the subgroups with or without uricemia in each group. The findings in the NHL and ALL patients with and without hyperuricemia were statistically compared using the t-test or chi-square test. Statistical comparisons were performed using SPSS v.10.0.

Results

Data obtained from a total of 327 newly diagnosed patients with NHL (n=113) and ALL (n=214) between December 1997 and January 2007 were examined. Table 2 shows the epidemiological and clinical characteristics of the patients. Mean age at the time of diagnosis was 6.5±5.2 years (range: 0.9-17.3 years) and 6.1±3.9 years (range: 1.16-17.5 years) in the NHL and ALL groups, respectively (P=0.8).

Among the patients with NHL, 68% (n=77) had B-cell, 28% (n=31) had lymphoblastic, and 4% (n=5) had anaplastic large cell lymphoma. According to the St. Jude staging system, 2.7%

(n=3), 77% (n=87), and 20.3% (n=23) had stage II, III, and III disease, respectively. Mean LDH level was 895±1246 IU/L , with 56% of the patients having an LDH level >500 IU/L. Among the ALL patients, 65% (n=139), 16.8% (n=36), and 18.2% (n=39) were in the standard-, medium-, and high-risk categories, respectively. Mean LDH level was 372±213 IU/L, and 12% (26/214) had an LDH level >500 IU/L. In all, 28 of the children with leukemia (13%) had a leukocyte count >50,000 mm^3 (range: 50,000-192,000 mm^3; mean: 82,985±39,029 mm^3). Mean serum urea, creatinine, and uric acid levels did not differ significantly between the NHL and ALL patients (Table 2).

Serum uric acid levels were above the normal range, corresponding to hyperuricemia in 30 children (26.5%) with NHL and 27 children (12.6%) with ALL (p=0.05). TLS criteria were met by 15.9% (n=18) of the NHL patients and 1 (0.47%) ALL patient (p=0.001). The majority of hyperuricemic NHL cases (25/30, 83%) presented at initial diagnosis, of which 5 (17%) developed hyperuricemia following the first dose of chemotherapy; the corresponding figures for hyperuricemic ALL patients were 59% (16/27) and 41% (11/27), respectively. A comparison of the characteristics of the hyperuricemic and normouricemic patients is shown in Table 3. All hyperuricemic NHL patients had stage III or IV disease, and their mean urea and creatinine concentrations were higher than those in the normouricemic cases (p=0.001

and p=0.001, respectively). In 96.6% of the hyperuricemic NHL patients LDH was >500 UI/L (mean concentration: 1286±1378 UI/L). LDH levels in the hyperuricemic cases were significantly higher than those in the normouricemic cases (p=0.001). Of the hyperuricemic NHL patients, 53% had renal involvement, as compared to 19% of the non-hyperuricemic NHL patients (p=0.001) (Table 3).

Among the hyperuricemic ALL patients, 59% and 41% were in the medium- and high-risk categories, respectively. Mean LDH was 967±798 UI/L, with 66.6% of the cases (18/27) having an LDH level >500 UI/L. All hyperuricemic ALL cases had an elevated white cell count, versus 1 (0.5%) patient in the non-hyperuricemic ALL group (p=0.0001). No patient had renal involvement. LDH levels were not significantly different between the NHL and ALL patients (p=0.29), nor were creatinine or urea (p=0.15 and p=0.8, respectively). Mean serum uric acid level in the hyperuricemic NHL and ALL patients was 13.29±5.92 mg/dL and 8.82±1.4 mg/dL, respectively (p=0.0001). The maximum uric acid concentration in these 2 groups was 30.4 mg/dL and 13 mg/dL, respectively.

Table 4 shows the TLS grading. None of the patient with TLS developed arrhythmia or seizure. Among the hyperuricemic NHL patients, renal involvement was observed in 77% and 25% of the cases that did and did not develop TLS, respectively (Fisher's exact test, p=0.008). Including the 1 ALL patient with TLS, in all 5 patients with TLS (26.3%) LTLS was diagnosed without clinical signs. Grade I, II, III, and IV CTLS was observed in 15.8%, 26.3%, 26.3%, and 5.3% of the patients, respectively. Routine treatment for hyperuricemia resulted in normalization of the uric acid level within 1-10 d. On average, normouricemia was achieved within 3.57±2.1 and 3.07±0.8 d in NHL and ALL patients, respectively (P=0.22) (Figure 1). All hyperuricemic ALL patients had their serum uric acid level normalized following the routine treatment protocol for hyperuricemia. Of the 30 NHL patients, 26 had their uric acid and other biochemical parameters normalized, while among the 4 patients that developed TLS (21%), 3 cases with grade III disease and 1 case with grade IV disease required hemodialysis due to refractory hyperphosphatemia and oligoanuria. Patients that required hemodialysis represented 7% (n=4/57) of the patient population with hyperurice-

Table 4. Cairo-Bishop grading results in the TLS cases

Grade (n=19)	n (%)
LTLS	5 (26.3)
Grade I	3 (15.8)
Grade II	5 (26.3)
Grade III	5 (26.3)
Grade IV	1 (5.3)
Grade V	-

LTLS: Laboratory tumor lysis syndrome

Table 3. Characteristics of the hyperuricemic and normouricemic patients

	NHL hyper-uricemic (n=30)	NHL non-hyper-uricemic (n=83)	P	ALL hyper-uricemic (n=27)	ALL non-hyper-uricemic (n=187)	P
LDH* (UI/L)	1286±1378	753±1170	0.04	967±798	286±194	0.01
High LDH** (n, %)	29 (96.6)	35 (42.2)	0.001	18 (66.6)	11 (5.9)	0.001
Uric Acid* (mg/dL)	13.29 5.92	3.76±1.33	0.0001	8.82±1.4	5.6±4.32	0.02
Urea* (mg/dL)	54.73±62	21.54±6.24	0.001	51.71±12	20.6±2.20	0.001
Creatinine* (mg/dL)	1.22±1.78	0.56±0.15	0.001	0.72±0.0 9 0.5±0.01	0.05	
Renal involvement (n, %)	16 (53)	16 (19)		0.001	-	-
High WBC† (n, %)	-		-	27 (100)	1 (0.5)	0.0001
TLS (n, %)		18 (60)		-1 (3.7)	-	
Recovery time* (days)	3.57±2.1	-	3.07±0.8	-	0.22	

*Mean ± SD, **High LDH: ≥500 IU/L , †High WBC: ≥50,000 mm^{-3}.
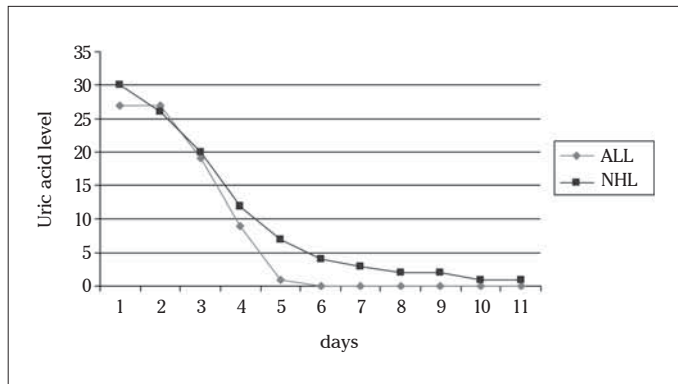
Figure 1. Comparison of serum uric acid level during treatment in NHL and ALL patients

mia. In the presented patient series no deaths were recorded during hyperuricemia or TLS.

Discussion

Hyperuricemia, which is the most common pediatric metabolic emergency, is a sign of TLS that occurs in high grade NHL, B-cell ALL, and acute myelocytic leukemia patients [1,2,7]; however, it has also been reported in some solid tumors, such as neuroblastomas and germ cell tumors. It can occur spontaneously or due to tumor lysis caused by a number of therapeutic modalities, including conventional cytotoxic chemotherapy, anti-CD20 monoclonal antibodies, and radiotherapy. It can also be triggered by administration of a single dose of steroid [1,2,6,8].

The reported frequency of hyperuricemia and TLS is primarily based on single-center studies, and varies between 5% and 42%. Patients with B-cell lymphoma or Burkitt's lymphoma were reported to experience this condition twice as frequently as patients with T-cell lymphoma [9-12]. In multi-center NHL trials of the BFM-90 and 95 protocols, 4.4% of the total study population (78 out of 1791) experienced TLS, which occurred in 8.4% of the patients in the Burkitt's lymphoma and B-cell ALL subgroups, versus 1.9% in the T-lymphoblastic lymphoma subgroup [11]. Metabolic catabolism was reported in 34 of the 410 patients (8%) with grade III and IV NHL, and B-cell ALL that were included in the LMB-89 protocol. Severe TLS was reported in 5% of patients and 1.7% required hemodialysis. In that series high tumor burden prevailed and 14% had renal involvement [13]. In a study from Turkey clinical signs and outcomes were reported for 97 NHL

patients, including 72 cases that received LMB-89 and 25 that received a modified LMT-89 protocol. Among these patients, 89.7% had stage III or IV disease, and 34 (35%) had TLS and hyperuricemia. Severe TLS was reported in 16.5% of the patients, of which 26% required hemodialysis [14].

Among patients with B-cell NHL that received a modified NHL BFM protocol, the reported incidence of TLS was 14% [15]. In the present study's sample 30 (26.5%) of the 113 NHL patients had hyperuricemia and 18 (15.9%) had TLS, which is consistent with previously published data, and can be explained on the basis of the similarities in the biological and clinical characteristics of the patients in Turkey. The high incidence of B-cell lymphomas and the transitional nature of Burkitt's lymphoma between the endemic and sporadic types result in a high number of advanced cases and increases the frequency of metabolic emergencies in Turkey [16,17]. This is similar to other reports from the same geographical location. For instance, TLS was reported in 22.5% of 59 patients with NHL, approximately 50% in the form of LTLS [18].

In patients with NHL and ALL tumor burden is associated with increased severity of hyperuricemia, while TLS or the need for hemodialysis is more likely to occur with renal involvement, which has been reported in 14%-61% of patients with TLS [13,15,19]. In the present study renal involvement occurred in 19% of the NHL patients and 53% of the hyperuricemic patients; this figure was 77% in the patients that developed TLS, as compared to 25% in those that did not (p=0.008). Renal involvement not only increases the risk of acute complications, but also has adverse consequences with regard to long-term prognosis [20]. None of the ALL patients in the present study had renal involvement. More severe hyperuricemia and a high incidence of TLS in the NHL group were probably associated with bulky disease accompanied by renal involvement.

Similar to risk stratification in lymphoma patients, cases with ALL and AML can be classified in terms of the risk of hyperuricemia. Hyperleukocytosis, B-cell ALL, bulky mediastinal masses, and high LDH levels are likely to be associated with increased risk of hyperuricemia in leukemic patients [1,10-13,21].

In the present study all the hyperuricemic ALL patients had high tumor burden and elevated leukocyte counts, and 66.6% had elevated LDH levels (≥500 UI/L), which highlights the importance of

tumor burden in ALL patients. To the best of our knowledge this is the first study from Turkey to compare the incidence of hyperuricemia and TLS in patients with NHL and ALL diagnosed at the same center. The present data show that there was a 2.1- and 33-fold increase in hyperuricemia and TLS, respectively, in children with NHL. These findings suggest that pediatric NHL patients with advanced disease and renal involvement represent the primary risk group for TLS.

Of the 19 TLS cases reported here, 26.3% (n:5) met the criteria for LTLS and none had CTLS. Among the other 14 cases, 15.8% and 26.3% were classified as grade I and grade II, respectively. The rest had grade III (26.3%) and grade IV (5.3%) CTLS. Additionally, the severity of CTLS correlated with the requirement for hemodialysis. The prognostic significance of this novel classification is yet unknown and to clarify this issue clinical outcomes should be assessed in prospective studies.

Despite previous reports of mortality and high hemodialysis rates associated with allopurinol treatment in TLS, in the present study high-risk patients were treated with hydration, alkalinization, and allopurinol, and no mortality associated with TLS was recorded. Additionally, none of the patients received urate oxidase and 7% required hemodialysis.

Substitution of allopurinol with urate oxidase has been reported to decrease the incidence and severity of TLS [22,23]. The cost-effectiveness of urate oxidase is a subject of continuing research worldwide [24]. Urate oxidase is administered with varying doses and durations, depending on the level of risk. The major advantages of urate oxidase are rapid fall in serum uric acid level after a single dose and no prerequisite for urinary alkalinization; however, high acquisition cost and hemolysis in patients with G6PD enzyme deficiency are the major drawbacks limiting its use [2,7,12,23]. In the present study serum uric acid levels returned to normal in a mean 3.5 d. We think that selective use of allopurinol is a rational approach in such cases when resources are limited.

Conflict of interest statement

None of the authors of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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