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Treatment of Pediatric Burkitt Lymphoma in Turkey

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Summary: This study aimed to assess the demographic data and treatment results of children who were diagnosed with Burkitt lymphoma and treated according to the Berlin-Frankfurt-Münster-95 (BFM) protocol in a single institution. A total of 48 patients (37 boys, 77%) with a median age of 8 years (range 2 to 16 years) at diagnosis, were evaluated. Primary tumor sites were abdomen (70.8%), head and neck (22.9%), peripheral lymph node (2%), bone (2%), and testis (2%). The 5-year overall survival (OS) and event-free survival (EFS) were 78.1 ± 4% and 76.6 ± 6%, respectively. In univariate analysis, hemoglobin level less than 10 g/dL, cerebrospinal fluid (CSF) positivity and dialysis requirement at diagnosis were found to be important reverse predictor factors for EFS (*P*; 0.001, 0.001, 0.004, respectively). In multivariate analysis, hemoglobin level less than 10 g/dL and dialysis at diagnosis were found to be important reverse predictor factors for EFS (*P*; 0.0001). The EFS of our patients was lower than the values achieved with BFM-95 protocol in other centers. This study provides evidence that low hemoglobin level, CSF positivity and dialysis at diagnosis were important predictor factors for EFS in children with Burkitt lymphoma.

Key Words: Burkitt's lymphoma, childhood, prognostic values

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Children and adolescents with non-Hodgkin lymphoma (NHL) have reached a satisfied prognosis with highly intensive chemotherapeutic regimens stratified according to histology and clinical stage.[1,2] Today, in most centers in developing countries, 75% to 90% of patients survive event free.[2–23] Although malignant lymphomas are the third most common malignancy in children in many countries, they are the second most common group of malignancies in Turkey.[24–27]

After 1990, children with NHL were treated with BFM (Berlin-Frankfurt-Münster-95) based protocols at our center. Since 1995, we use the protocol BFM-B cell NHL-95 in patients with Burkitt lymphoma. This study was carried out to assess the demographic data and treatment results of children who were diagnosed with Burkitt lymphoma and treated according to the BFM-B cell NHL-95 protocol in our institute. We aimed to present our experience with this protocol and to compare our data with the results from other centers.

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PATIENTS AND METHODS

Patients

A total of 48 patients younger than 18 years old with newly diagnosed Burkitt lymphoma were treated in our department with BFM NHL-95 protocol between September 1995 and December 2007 were included to the study. Patients with immunodeficiency, anaplastic large cell lymphoma, MALT lymphoma, and patients treated earlier for any form of cancer or by transplantation were excluded. The disease was diagnosed by cytomorphology/immunuphenotyping of bone marrow/malignant effusions or biopsy specimen of lympadenopathy/tumor and classified according to the updated Kiel classification for B-NHL.[28]

Staging, Stratification of Treatment Intensity, Chemotherapy, and Response Criteria

The St. Jude staging system was used for clinical staging.[2] The staging studies included patient history, physical examination, complete blood count, peripheral blood smear, serum chemistry including serum lactate dehydrogenase (LDH), bone marrow (BM) aspiration smears, cerebrospinal fluid (CSF) analyses, ultrasonography, X-ray, computed tomography (CT) or magnetic resonance imaging (MRI), bone scintigraphy and recently, positron emission tomography (PET). Extramedullary, testis, and CSF involvement were defined as published by Patte et al.[18,19] The patients were stratified into 4 risk groups according to stage, resection status, pretherapeutic serum LDH, and the presence of central nervous system (CNS) disease according to the protocol.[20]

Hydration with 3000 mL/m^2/d fluids, alkalization with $NaHCO_3$ intravenously, allopurinol, and forced diuresis were administered to prevent tumor lysis syndrome (TLS). Recombinant urate oxidase could only be provided in 5 patients owing to inavailability of the drug.

Patients in risk groups R2, R3, and R4 according to the protocol received a cytoreductive prophase treatment including steroids and cyclophosphamide before the first course (A or AA) of induction treatment.[20] Methotrexate (MTX) was administered by intravenous infusion over 24 hours continuously. The dose of MTX was 1 g/m^2 in courses A and B (risk groups R1, R2), and 5 g/m^2 in courses AA, BB (risk groups R3, R4). Patients received 2 courses of induction therapy in risk group R1 (resected), 4 courses in R2 (LDH < 500 U/L), 5 in R3 (LDH > 500 to < 1000 U/L) and 6 in R4 (LDH > 1000 U/L and/or CNS disease).[20]

Tumor response was evaluated after the second therapy course. Complete remission (CR) was defined as the clinical disappearance of disease, confirmed by computed tomography (CT) scan, BM and CSF evaluation. Partial remission (PR) was defined as more than 50% of tumor regression. Progressive disease (PD) was defined by the appearance of new disease during treatment or as incomplete regression of local tumor followed by progression during chemotherapy. Relapse was defined as evidence of disease after 1 month in CR.

In patients with BM and/or CNS involvement, follow-up bone marrow aspiration (BMA) and/or lumbar puncture were carried out until BM and/or CNS were free of blasts. The number and duration of febrile neutropenia episodes during treatment were recorded. Throat, blood and urine cultures, and cultures of possible sites that could be source of infection were obtained during each febrile neutropenia attack. The chemotherapy-related side effects, infections, and transfusions were also recorded. Follow-up studies were conducted at 4-week intervals in first year of CR.

Statistical Methods

Event-free survival (EFS) was determined as the time from the initial treatment to relapse, progression, death, or the most recent follow-up examination. Overall survival (OS) was calculated from the initiation of treatment to death or the last follow-up examination. Differences in the distribution of individual parameters among patients were analyzed using the χ^2 test or Fisher Exact Test. Analyses of EFS and OS were done using the Kaplan-Meier method with differences compared by the log-rank test. Multivariate analysis using Cox proportional hazard regression method was completed to determine the independent prognostic factors influencing EFS. Pretherapeutic factors that were identified as significant for EFS by univariate analysis were included in multivariate analysis. All calculations were done with SPSS version 13.0 statistical software.

RESULTS

Patients

The clinicopathologic features of the 48 patients are shown in Table 1. Thirty-seven (77%) patients were boys and the mean age at diagnosis was 8.33 ± 3.82 years. Primary tumor sites were abdomen in 34 patients (70.8%), head and neck in 11 (22.9%), and 1 patient (2%) each in peripheral lymph node, bone, and testis. Bone marrow and CNS involvement were detected in 12 (25%), and 5 (10.4%) patients, respectively. According to the St. Jude staging system, 1 patient was classified as stage I; 6 as stage II; 23 as stage III, and 18 as stage IV. Eighty-five percent of the patients (41/48) had advanced disease. The level of LDH was < 500 U/L in 13 (27%) patients, between 500 to 1000 U/L in 15 (31.2%) and > 1000 U/L in 20 (21.6%). Four (8.3%) patients were classified in risk group RI, 7 (14.5%) patients in group R2, 13 (27%) patients in group R3, and 24 (50%) in risk group 4 (Table 2).

Treatment Results

Of the 48 patients, CR was achieved in 36 (75%) and PR in 3 (6.2%). In the whole group, 11 (22.9%) patients died. Nine (18.7%) died before remission owing to toxic side effects of the treatment (6 patients from TLS and 3 patients from infection during febrile neutropenia). Extended spectrum β lactamase (ESBL) positive *Escherichia coli* and *Klebsiella pneumonia* were isolated in blood cultures of 3 patients. Two patients had lung hemorrhages

TABLE 1. The Clinicopathologic Features of the Patients

	Parameters		
Findings	**Alive (n: 37)**	**Dead (n: 11)**	***P***
Age of diagnosis	8.26 ± 3.43 y	7.30 ± 5.03 y	0.47
Sex	30 (%81.1) male, 7 (%18.9) female	7 (63.6%) male, 4 (36.4%) female	0.24
Primary tumor site			
Abdomen	25 (67.5%)	9 (81.1%)	0.46
Head-neck	10 (27.0%)	1 (9.0%)	
Peripheral node	1 (2.7%)	—	
Bone	1 (2.7%)	—	
Testis	—	1 (9.0%)	
Laboratory			
WBC ($\times 10^3$/mm^3)	10316 ± 8910	10780 ± 4862	0.87
PNL ($\times 10^3$/mm^3)	6000 ± 4980	7020 ± 5388	0.56
Hb (g/dL)	11.1 ± 2.2	9.2 ± 2.4	**0.02**
Uric acid (mg/dL)	4.1 ± 2.9	5.3 ± 3.2	0.25
LDH (IU/L)	770 (30-2500)	1700 (268-8520)	0.85
Stage			
	S1: 1 (2.7%)	—	0.12
	S2: 6 (16.2%)	—	
	S3: 18 (48.6%)	S3: 5 (45.4%)	
	S4: 12 (32.4%)	S4: 6 (54.5%)	
Dialysis	3 (%8.1)	6 (%54.5)	**0.001**
Bone marrow involvement	9 (%24.3)	3 (%27.2)	0.44
CSF involvement	1 (%2.7)	4 (%36.3)	**0.01**
Tumor lysis syndrome	3 (%8.1)	9 (81.1%)	**0.0001**

BM indicates bone marrow; CSF, cerebrospinal fluid; Hb, Hemoglobin; LDH, lactate dehydrogenase; PNL, polymorphonuclear leukocyte; WBC, white blood cell.

TABLE 2. EFS Rates According to LDH Levels and Risk Groups

	Patients (n: 48)	EFS ± SE %
LDH level (U/L) < 500	13 (27%)	91.7 ± 8*
LDH level (U/L)500-1000	15 (31.2%)	71.1 ± 7*
> 1000	20 (41.6%)	
R1	4 (8.3%)	100
R2	7 (14.5%)	83.3 ± 15
R3	13 (27%)	76.9 ± 11
R4	24 (50%)	70.8 ± 9

*($P = 0.14$ LDH < or > 500U/L).
SE indicates standard error.

and toxic epidermal necrolysis, *Staphylococcus aureus* was isolated in blood cultures of these 2 patients. All toxic deaths occurred during the neutropenic phase after the first course of therapy. In patients with CR (36; 75%); only one relapsed at the primary tumor site (abdomen) 5 months after the end of treatment. This patient died owing to lung and gastrointestinal hemorrhage during second treatment period in BB course. In patients with PR (3; 6.2%); one patient's residual disease was resected and showed necrosis, and he has been in complete remission for 3 years, now. The second patient with PR was treated with anti-CD-20 monoclonal antibody (rituximab); however the patient died owing to progressive disease after second CC course and the third patient was treated again with chemotherapy for relapse and has been in complete remission for 10 years.

Central Nervous System Involvement

The CSF involvement was present in only 1 patient who survived, the other 4 patients with CSF involvement died ($P = 0.01$). Of these patients, 3 had CSF involvement at the time of diagnosis and 1 had at relapse.

Laboratory Findings

When the complete blood count, hemoglobin (Hb), neutrophil, uric acid, and LDH levels were evaluated, only the hemoglobin level was found to be significant for prognosis. The hemoglobin levels at the time of diagnosis of the patients who died were significantly lower ($P = 0.02$) compared with the patients who survived. The mean 5 year EFS in patients with Hb level < 10 g/dL was 45.7 ± 15%, whereas in those with Hb level > 10 g/dL was 86.1 ± 5%.

Survival

At a median follow-up of 51 months (range 15 to 158), the mean 5-year OS and EFS were 78.1 ± 4% and 76.6 ± 6%, respectively (Fig. 1). The mean EFS at 5 years was 100%, 83.3 ± 15%, 76.9 ± 11%, 70.8 ± 9% for patients in risk groups R1, R2, R3, and R4, respectively (Fig. 2). There was no significant difference in risk groups of the 11 patients who died, 1 was in R2, 3 in R3, and 7 in R4 group.

Univariate and Multivariate Analyses

Factors affecting the 5-year EFS were determined by univariate and multivariate analysis. In univariate analysis, hemoglobin level less than 10 g/dL, CSF involvement, and dialysis at diagnosis were found to be important reverse predictor factors for EFS (*P*; 0.001, 0.001, 0.004, respectively). There was no significant correlation between age, gender, LDH level, risk group or bone involvement and survival rates.

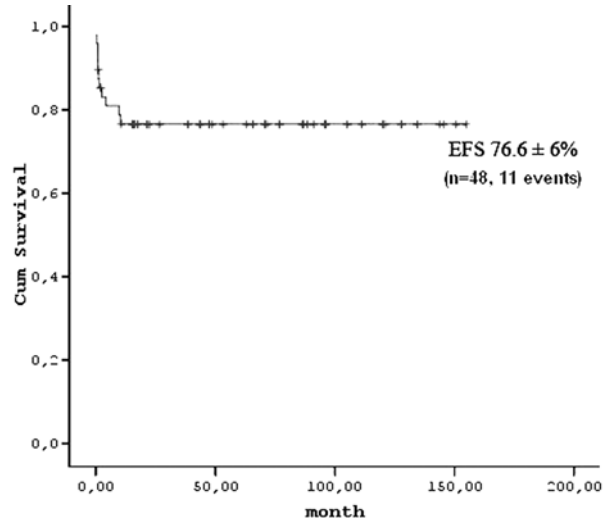

FIGURE 1. Kaplan-Meier estimate of event-free survival (EFS) of the whole group.

In multivariate analysis, hemoglobin level less than 10 g/dL and dialyses at diagnosis together were found to be important reverse predictor factors for EFS [*P*; 0.0001, 95% confidence interval (CI) for odd ratio: 1.30-5.06 and 1.17-4.44, respectively].

Treatment-related Toxicity

During prophase, 12 patients (25%) developed TLS; all of them had advanced stage disease (stage III or IV). Nine of the 12 patients required dialysis, 6 owing to intractable hyperuricemia, and 3 owing to hyperphosphatemia, and despite dialysis, 6 of these patients died. The other 3 were successfully managed by intensive hydration, alkalization with $NaHCO_3$, and allopurinol with forced diuresis after the first course of therapy. In 5 patients who were given recombinant urate oxidase, hyperuricemia was treated successfully; however 3 of them underwent dialysis owing to hyperphosphatemia. Myelosuppression was the main treatment-related complication, especially during courses AA, BB, and CC. Grade 3 to 4 hematologic toxicity occurred in all patients in R3 and R4 risk groups

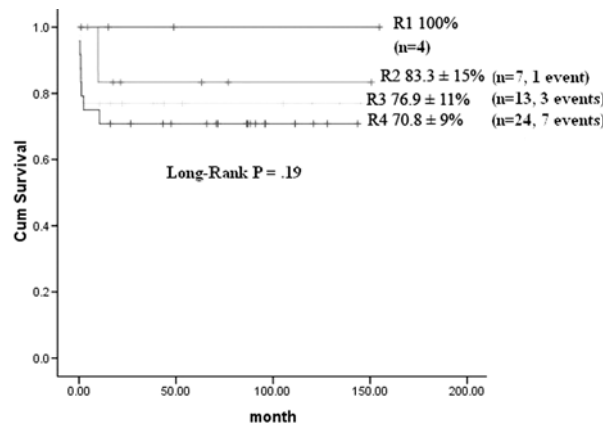

FIGURE 2. Kaplan-Meier estimate of event-free survival (EFS) owing to risk groups.

after each course of chemotherapy. Sixty-five percent of the patients required erythrocyte and/or platelet transfusions. In risk groups 3 and 4, growth granulocyte colony-stimulating factors were used at a dose of 5 μ/kg for 8 to 12 days. The mean duration of neutropenia was 5.8 ± 2.3 days. Mucositis was the most common side effect and was related to the methotrexate (MTX) dose, often developed in AA and BB courses with high dosage HD-MTX (5 g/m^2). Febrile neutropenia episodes were observed in 46 patients and 110 episodes of febrile neutropenia occurred in 4 (3.6%), 2 (1.8%), 44 (40%), 32 (29%), and 28 (25.4%) of A, B, AA, BB, and CC courses, respectively. Clinically, mucositis was the most common localized infection, followed by pneumonia. In 47% of the febrile neutropenic attacks there was no microbiologic verification whereas in 26%, microbiologic cultures were found to be positive. There were 27 isolated microorganisms from cultures, 11 were Gram (+) bacteria and 16 were Gram (−) bacteria. Ten of them were isolated from blood, 10 from urine, 5 from stool, and 2 from skin abscesses. In 19 episodes (17.3%) neutropenia was longer than 10 days, in 14 (12.7%) fever was longer than 10 days. All of the patients that died were from risk groups 3 or 4, and all were lost during or just after the first intensive chemotherapy block during neutropenia, with absolute neutrophil counts (ANC) of $< 500/mm^3$ and with a mean neutropenic period of 9.7 ± 2.8 day. A mean 10.1 ± 3.1 days of fever were recorded until death in these patients. A significant difference was found between patients that died or survived according to dialysis, CSF involvement, fever more than 10 days and culture positivity (*P*; 0.001, 0.01, 0.01, and 0.02, respectively).

DISCUSSION

Since the identification of different NHL subtypes, major advances have been made in the treatment of childhood NHL.[1–3,12,29] A strategy of rapidly repeated, short, dose-intense course treatment was proved to be more efficacious in children with B-NHL with EFS rates of up to 90%, although the chance to survive after relapse is still dismal.[12,29,30] In our current study the mean 5-year OS and EFS were found to be 78.1 ± 4% and 76.6 ± 6%, respectively. Major cooperative groups including Children's Cancer Group (CCG), Pediatric Oncology Group (POG), French Pediatric Oncology Society (SFOP), and BFM group have contributed greatly to the achievements in the treatment of pediatric NHL. The EFS-OS values of children treated for Burkitt lymphoma by different groups in different countries are shown in Table 3. Favorable results have been reported from different studies in childhood Burkitt lymphomas. Our OS and EFS rate results were lower compared with results of BFM,[20] SFOP,[18,19] and CCG.[12] Equivalent results were achieved with the other developing countries.[6,9,11,23] The reason for the differences in treatment results of various countries may be related to financial factors, delay in admission of the patients to reference centers, hospital infections, and the conditions of the different hospitals. There may be also a difference related to the protocols applied. The most important factors affecting the lower survival rate of our patients are the advanced stage of patients at admission and drug toxicity complicated with infections. The reports from Turkey have similar outcomes with similar problems.[24–27] High-dose MTX is one of the main reasons for toxicities.[20] More advanced disease presentations at diagnosis could have predisposed patients to more therapy-related complications/deaths. The efficacy and the toxicity of MTX in future protocols especially in developing countries must be clarified carefully.

In our series, according to the St. Jude staging system, one patient was classified as stage I; 6 as stage II; 23 as stage III, and 18 as stage IV. Eighty-five percent of the patients (41/48) had advanced disease. The other reports from Turkey had similar stages at admission. In the study by Karadeniz et al,[25] 77% (47/61 patients) of patients had advanced disease. According to BFM-95 protocol, most patients were in stage II and III (67%), 16 patients (3%) were in stage IV.[17] In various studies conducted in developing countries, patients were observed to admit at advanced stages,[9,13] mostly in stage III, consistent with our study. Early reference of the patients will provide better treatment results.

TABLE 3. Burkitt Lymphoma Results From Different Countries

Study	Country	No. Patients	Time Period	Treatment Protocol	OS%	EFS%
Current study	Turkey	48	1995-2007	BFM-95	78.1	76.6
Karadeniz et al[25]	Turkey	61	1993-2003	BFM-90, 95	85.8	82.8
Kutluk et al[26]	Turkey	97	1994-1997	LMB-89	75	
Reiter et al[3]	Germany	111	1986-1990	BFM-86	81	
Hesseling et al[5]	Malawi	42	2000-2002	COP/ COMP regimen		33
Chantada et al[6]; MTX: 2 g	Argentina	44	1988-1993	BFM-86		70
Kavan et al[8]	Czech rep.	21	1991-1997	BFM-90		57
Chantada et al[11]	Argentina	57	1994-1999	BFM-90	81	79
Cairo et al[12]	USA	46	1991-1995	Orange/ LMB-89		80
Pillon et al[14]	Italy	105	1992-1997	AIEOP-LNH 92		87.5
Sun et al[15]	China	22	1997-2005	BFM-90		85
Burkhardt et al[16]	Germany	1004	1986-2002	BFM-86, 90, 95		87
Patte et al[18]	France	420	1989-1996	LMB-89		92
Patte et al[19]	France	397	1996-2001	LMB-96		93.3
Marky et al[21]	Nordic countries	121	1995-2000	NOPHONHL-95	91	91
Wessels and Bernard Hesseling[23]	S. Africa	63	1983-2002	COMP, LMB-89, 96		25-87

AIEOP-LNH indicates the Italian Association of Pediatric Hematology and Oncology; BFM, Berlin-Frankfurt-Münster; COP/COMP, Cyclophosphamide, Vincristine, Prednisone/Cyclophosphamide, Vincristine, Methotrexate, Prednisone; EFS, Event free survey; LMB, Lymphomes Malins B; MTX, Methotrexate; NOPHO, Nordic Society of Pediatric Hematology and Oncology; OS, Overall survey.

The EFS in the present report is significantly compromised by deaths related to toxic side effects of the treatment. High-dose MTX, the back-bone of most leukemia/lymphoma protocols, is one of the main causes of treatment associated toxicities.[20] Apart from myelosuppression, mucositis was the leading toxic side effect. All toxic deaths occurred during the neutropenic phase after the first course of therapy (9 out of 11 patients). In the BFM 90 study, 6 of 9 deaths occurred after the first course similar to our results.[29] In groups using protocols like NHL-BFM 95, only 1 child died of TLS whereas 10 children died of sepsis (1.8%). Six of 10 deaths were after the first course.[20] The significant death rate with NHL-BFM 95 protocol was attributed to the advanced stage of most of the cases, myelosuppresion, and increased frequency of infection with higher MTX doses. Early diagnosis and urgent start of antibiotics for infections will diminish the rate of toxic deaths owing to infections.

CNS involvement was associated with an advanced stage of NHL.[31] In BFM-NHL study conducted between 1986 and 2002, CNS involvement was diagnosed in 141 (5.9%) of 2381 patients.[32] The percentage of CNS-positive patients was higher in B-cell type (8.8%). The mean EFS at 5 years was 85% ± 1% for the whole group whereas in the 112 CNS-positive patients, mean EFS was 64% ± 5% ($P < 0.001$). In multivariate analysis, it was shown that CNS involvement was the strongest predictor for relapse in BL/B-ALL patients with advanced-stage disease. Our results were similar with the BFM cohort, CSF involvement was associated with a poor prognosis (4 of the 11 patients that died had CSF involvement, 3 at diagnosis and 1 after relapse).

A tumor lysis syndrome, just like CSF involvement, was another factor that has influenced the prognosis of B-cell lymphoma.[33] In our cohort, 12 patients, all with advanced stage, developed TLS (25%), 9 required dialysis and despite dialysis, 6 (50%) of them died. In Wössmann's study, of 1791 children who were treated with BFM-based protocols, 78 children (4.4%) developed TLS.[17] In another study, including 1192 patients, 63 (5.2%) were reported to have suffered from impaired renal function and/or TLS before or during initial treatment; 58 (92%) of these patients had advanced stages of disease and high LDH-levels (> 500 U/L), 25 (40%) patients required hemodialysis and 9 of 63 patients (14%) with TLS died.[33] Another group in another developing country, Venezuela, used LMB-89 protocol and 9 (9%) patients developed TLS, 4 died (44%).[13]

In our study, the results did not reveal any significant difference in EFS according to LDH (< or > 500), however, all TLS occurred in advanced stage of disease. High LDH and advanced stage are warnings for TLS and supportive treatment is important in these patients. Many studies have showed that the prophylactic use of urate oxidase decrease TLS from 16.1% to 12.3%.[17] Unfortunately, urate oxidase is not available in all countries and could be used in only 5 patients in our study.

In this study, the hemoglobin levels at the time of diagnosis of patients who died was significantly lower ($P = 0.02$). In patients with hemoglobin level < 10 g/dL, EFS at 5 years was lower than those with > 10 g/d. In the univariate analysis, hemoglobin level less than 10 g/dL was found to be an important reverse predictor factor for EFS. In the multivariate analysis, hemoglobin level less than 10 g/dL and dialyses at diagnosis together were found to be important reverse predictor factors for EFS. The inverse relation between LDH level and EFS that was displayed in earlier studies was not shown in our study; however, the hemoglobin level as a negative predictor factor was found to be important in prognosis.

In conclusion, despite treatment success rates being lower than those reported by BFM-95 protocol, BFM-based NHL protocols for B-cell NHL in children are successful regimens even in developing countries. Inferior outcomes might be related to advanced stage, delay in admission to treatment center, and infectious problems. Moreover, hemoglobin level less than 10 g/dL, CSF involvement, and dialyses at diagnosis were found to be important reverse predictor factors for EFS.

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