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Original Article

Treatment results of modified BFM protocol in pediatric high-risk Burkitt lymphoma

Sema Vural[1], Dildar Bahar Genç[1], Rejin Kebudi[2], Öner Doğan[3], Serap Karaman[2]

[1]Department of Pediatric Oncology, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, İstanbul; [2]Department of Pediatric Hematology/Oncology, Istanbul University Institute of Oncology, İstanbul; [3]Department of Pathology, İstanbul University Medical Faculty, İstanbul, Turkey.

ABSTRACT

Background. Chemotherapy with high dose methotrexate is the mainstay of treatment for Burkitt lymphoma (BL), especially to manage central nervous system (CNS) disease. However, methotrexate administration requires close drug level monitoring for appropriate folinic acid rescue, which might not be readily available in all centers. In this study, we assessed the long-term treatment outcomes of a modified Non-Hodgkin lymphoma (NHL)-Berlin-Frankfurt-Munster (BFM) 90 regimen in pediatric high-risk BL without CNS involvement.

Methods. Between 1999 and 2011, 42 patients (median age: 7 years) with advanced-stage BL were treated with modified NHL-BFM 90 regimen (methotrexate at a dose of 1 g/m^2). Demographic data, stage, lactate dehydrogenase (LDH) and treatment results were retrospectively evaluated. The patients were assessed for toxicity, survival and CNS recurrence.

Results. Thirty-six patients had Stage III and six had Stage IV disease, respectively. The median LDH level was 1,432 IU/L. Four patients died of infectious and metabolic complications. One patient had local recurrence at the 48th month of the follow-up and he is in the second remission for 72 months. In Kaplan-Meier analysis, the overall survival and event-free survival rates at 10 years were found as 90 % and 88 %, respectively. None of our patients died of treatment failure.

Conclusions. The administration of the reduced dose of methotrexate seems to not compromise treatment success nor increase the risk of CNS recurrence in high-risk BL without CNS involvement. The limitation of the study is that it is not randomized. Our treatment scheme might be considered for centers without methotrexate measurement facility.

Key words: Burkitt lymphoma, BFM, methotrexate.

Lymphomas constitute the third most frequent cancer of children in developed countries.[1] However, in developing countries including Turkey, lymphomas (with a percentage of 18.1%) are the second most common malignancy following leukemia.[2] Burkitt lymphoma (BL) cases benefit from intensive short pulse chemotherapy[3] and the treatment intensity is tailored according to previously defined risk factors. Depending on the protocol, risk group (RG) definitions may vary.[1] Generally, the patients with advanced stage disease, elevated lactate dehydrogenase (LDH) levels and/or central nervous system (CNS)/bone marrow (BM) involvement are assigned to high risk (HR) groups (Table I).

For HR patients enrolled in NHL (Non-Hodgkin lymphoma)-BFM (Berlin-Frankfurt-Munster) and other collaborative groups' protocols, HD-Methotrexate (MTX) (3-8 g/m^2) administration has led to remarkable survival advantage possibly by increasing drug penetrance into

✉ Dildar Bahar Genç
baharbeker@yahoo.com

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Table I. Risk stratification according to NHL-BFM 90 and NHL-BFM 95 studies.

NHL BFM 90[4]	R3	*Stage III + LDH≥500 U/L, *Bone marrow involvement *CNS involvement *Multifocal bone lesions
NHL BFM 95[25]	R3	*Stage III and LDH >500, <1000 U/L *Stage IV+B-AL and LDH<1000 U/L and CNS involvement (-)
	R4	*Stage III and IV and B-AL and LDH>1000 U/L *CNS involvement

CNS: Central nervous system

sanctuary sites like CNS.[4,5] However, serum drug level monitoring as well as status of methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms is crucial for safe and effective HD-MTX administration to install a proper folinic acid (FA) rescue schedule.[6] Overdosed FA rescue might abolish the anti-proliferative activity of MTX whereas inadequate doses of FA might lead to increased toxicity.[7-9] In one of the studies reported from our country, NHL high-risk patients were treated with 5 g/m^2 MTX schedule (NHL-BFM 90 protocol) and FA was empirically administered due to lack of MTX measurement facility. The treatment-related toxicity was high and significant treatment delays were observed between the chemotherapy blocks. Increased mortality due to toxicity and recurrent disease led to lower survival rates in comparison to results of the original BFM studies.[10] Therefore, the dose of MTX was reduced to 1g/m^2 in high-risk BL patients without CNS involvement. This study aims to assess the results of the modified NHL-BFM 90 protocol by decreasing the MTX dose from 5 g/m^2 to 1 g/m^2 in HR BL patients without CNS involvement in a developing country.

Material and Methods

Patient eligibility: All HR BL patients without CNS involvement aged younger than 18 years and treated in our center, between 1999 and 2011 were eligible. Disease stage and risk group (RG) stratification were determined according to criteria described in NHL-BFM 90 protocol. Risk group 3 (advanced stage) included the patients with Stage III (St. Jude) and LDH≥500 U/L or/and patients with bone marrow involvement or/and central nervous system disease or/and multifocal bone lesions.[4] Patients with CNS involvement, patients treated with higher doses of MTX (i.e. 5 g/m^2) and patients in the medium risk group were excluded.

Data collection: Patients' files were retrospectively reviewed. Age, gender, stage, site of primary involvement, diagnostic method, LDH, RG, treatment response, toxicity and disease status were recorded. There was no missing data, and no bias in patient selection. Consent was obtained from the parents.

Pretreatment work-up: A histopathological diagnosis was obtained in all patients. BL was diagnosed by the integration of morphological, immune-phenotypic and genetic studies. Routine chemistry profile, chest x-ray, abdominal ultrasound, BM examination, spinal fluid analyses, computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site and metastatic sites were performed.

Treatment protocol: Patients received six cycles of chemotherapy based on the NHL- BFM 90 protocol. The details of the original treatment scheme have been reported previously.[4] MTX was administered as 1 g/m^2/36 hours in our study instead of 5 g/m^2/24 hours, which is the dose described in the original protocol. Ten percent and the rest of the dose were infused within 30 minutes and 35.5 hours, respectively. Racemic FA (15 mg/m^2) was empirically administered at

48 and 54 hours after the beginning of the MTX infusion. In the course CC, vincristine (1.5 mg/m^2) was administered instead of vindesine due to its unavailability in Turkey. Requirements for the start of chemotherapy (except for the first course) were as follows: Neutrophil counts higher than 500/mm^3 and platelet counts higher than 50.000/mm^3 after the nadir of post-chemotherapeutic cytopenia has resolved. The minimal and maximal interval between successive chemotherapy blocks were two and three weeks, respectively.

Toxicity and response assessment: Toxicity was evaluated in accordance with World Health Organization (WHO) Criteria.[11] Tumor response to therapy was evaluated after each course of therapy by physical examination, biochemistry, and abdominal ultrasound. In patients with BM involvement, control BM examination was performed until the BM was cleared from blasts. After two blocks of chemotherapy, abdominal CT or MRI was also done.

Complete remission (CR) was defined as the clinical disappearance of the disease. Partial remission (PR) was accepted 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 the treatment protocol. Relapse was defined as evidence of disease after at least 1 month in CR.

Ethics Approval

The study is approved by our Hospital Ethics Committee (University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee-Number 3003/2020).

Statistical Analysis:

Patient characteristics were summarized using descriptive statistics. Last evaluations were conducted in December 2017. Event- free survival (EFS) was calculated from the day of diagnosis to the date of last observation without events (relapse, secondary malignancy, and death from any cause). Overall survival (OS) was the time interval between the date of diagnosis and the date of death from any cause or the date of the last follow-up on which the patient was known to be alive. The survival estimates were assessed by the Kaplan-Meier method. Survival was censored at the date of the last follow-up if death was not observed. A p value < 0.05 was statistically significant.

Results

Patient's characteristics: During the study period, 55 children with BL were treated. Two patients with CNS involvement, 11 patients in the medium risk groups were not eligible. Forty-two patients were included in the study. Seventy percent of the patients were referred from cities other than Istanbul. Thirty-four boys and eight girls had a median age of 7 years (range 3-14 years). The abdomen was the most common site of primary involvement and laparotomy was the most frequent method for diagnostic tissue sampling. Thirty-six patients had Stage III and six had Stage IV disease, respectively, with a median LDH value of 1432 U/L (550 - 9080) (Table II). All the patients came from families of lower socioeconomic status (had income equal to or below the minimum wage).

Outcome: We did not observe treatment failure-related mortality during the study period. Two patients died during prophase due to sepsis and one patient died after the first AA block due to sepsis and tumor lysis syndrome. The remaining 39 patients were evaluated for treatment response after 2 courses (AA+BB) of chemotherapy. Twenty-eight (72%) patients achieved CR and 11 patients had a PR (28%). Two patients had radiological evidence of residual lesions after completing the treatment. The pathological examination of resected residual masses revealed complete necrosis in all cases. One patient in remission died of neutropenic fever and sepsis after the last course of treatment. We observed one case of local (abdominal) recurrence at the 48th month of the follow-up and the patient was salvaged by second-line chemotherapy. He has been in

remission for 72 months since the recurrence date. All the remaining 38 patients are alive with no evidence of disease. In Kaplan-Meier analysis, the OS and EFS rates at 10 years were found as 90 % and 88 %, respectively (median follow-up of 121 months (one week-210 months) (Fig. 1). The most common treatment-related adverse effect was grade III and grade IV hematological toxicity (79%). Febrile neutropenia was observed after 70% of chemotherapy blocks. Severe mucositis was seen in 42% of courses.

Table II. Clinical and demographic data of patients.

Factor	Results
Age-Median (range)	7 years (3-14 years)
Sex	
Female	8
Male	34
Primary tumor site	
Abdomen only	36
Abdomen and cervical lymph node	2
Abdomen and orbita	1
Abdomen and jaw	1
Abdomen and tonsil	1
Abdomen and paravertebral area	1
Stage	
III	36
IV	6
LDH -Median (range)	1432 (550-9080) IU/L
Diagnostic procedure	
Laparotomy	16
Tru-cut biopsy	13
Excisional/incisional biopsy	4
Fine needle biopsy	1
Peritoneal fluid cytology	7
Bone marrow aspiration	1

Discussion

Patients with mature B cell lymphomas have been treated with chemotherapy protocols of varying intensity and duration according to the assigned risk groups.[4,5] A comparison in terms of treatment success across the study groups is quite difficult since the risk stratification and chemotherapy protocols are not uniform. In the present study, 80% of our BL patients were in the RG3 group according to NHL-BFM 90 risk criteria. The percentage of RG3 patients was quite high in our study, in comparison to that of the original BFM 90 series (43%). Even if we were to stratify our patients according to NHL-BFM 95 protocol, the percentage of our RG3 and RG4 patients would have still been higher than that of the original BFM NHL 95 protocol (18 % and 64% vs. 16% and 28%, respectively).[4,12] Our RG distribution appears to be similar to that of other developing countries.[13-15] The number of

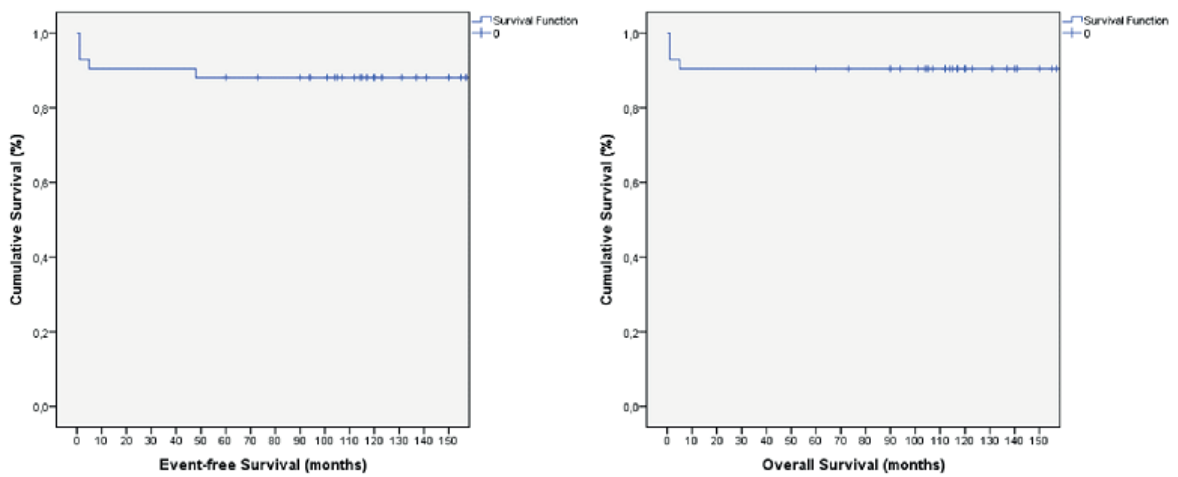

Fig. 1. Survival curves of high-risk CNS-negative patients treated according to modified BFM approach.

HR patients in our country differs according to the city and to the center of the study.[16,17] During the period of the study, our center admitted patients of low socioeconomic status, and most of the patients were referred from medically underserved rural areas of Turkey. Most of the severely ill patients were transferred under inappropriate conditions and most patients underwent unnecessary laparotomy leading to delayed referral. The above circumstances might have contributed to the higher number of advanced stage patients.

The MTX dose and the duration of administration are not standard among different BL protocols, and the optimal dose and the duration of MTX infusion are not clear.[4,5] This issue raises the question of whether the higher doses of MTX (e.g. 5-8 g/m^2/cycle) are essential in the treatment of BL. High-dose MTX chemotherapy necessitates stringent supportive care and appropriate folinic acid administration adjusted according to serum levels of MTX. Lack of these measures might increase toxicity and lead to prolonged intervals between the cycles with inferior treatment outcomes. The lower doses of MTX administration have been especially preferred in centers without MTX level measurement facilities.[17-20]

Due to methodological differences between the studies with modified protocols, it is not possible to make a reliable comparison among these studies as well as with the original BFM study. Although some study groups did not present subgroup (i.e. RG) analysis data in their reports, the EFS or OS rates were reported to range between 50-82% in modified BFM protocols with 1-2 g/m^2 MTX, with or without Rituximab (Table III). In our study, the EFS rate was 89 % with 1 g/m^2 MTX without rituximab in all our RG3 patients without CNS involvement. The survival rate of our patients seems comparable to the results reported from BFM groups (which used MTX 5 g/m^2 (NHL-BFM 90 R3 Stage III 81%, and NHL-BFM 95 R3 85±4%, R4 81±4%))[4,12] and seems superior than the survival rates of several studies with 5 g/m^2 MTX from developing countries and Turkey (Table III).[13,14,16,17,20-23]

Table III. Doses of methotrexate and treatment outcomes of previous BFM-based studies with high-risk Burkitt lymphoma.

Authors	Country	Protocol	MTX (g/m^2/course)	EFS	OS
Reiter A et al.[4]	International	BFM 90	5	78	
Woessmann et al.[25]	International	BFM 95	5	81	
Kavan et al.[26]	Czech Republic	BFM 90	5	57*	
Müller et al.[27]	Hungary	BFM 90/95	5	81	83
Pillon et al.[28]	Italy	AIEOP LNH92 (BFM 90)	5	73	
Celkan et al.[16]	Turkey	BFM 90	5	71	
Karadeniz et al.[17]	Turkey	Modified BFM 90	1	80*	81*
		Modified BFM 90	3	92*	92*
		Modified BFM 95	5		
Kebudi et al.[18]	Turkey	BFM 90	5	44*	44
		Modified BFM 90/95	1	69*	81*
Sun al.[29]	China	Modified BFM-90	5	72	
Cervio et al.[30]	Argentina	Modified BFM 90/95	2	70	
Chantada et al.[31]	Argentina	Modified BFM-90	2	82-50 (RG3-4)	81*
Klumb et al.[20]	Brazil	Modified BFM 90	2	74	
Márky al.[32]	Nordic countries	NOPHO 95, BFM 90-95	5	91*	
Dokmanovic et al.[33]	Serbia	BFM 95	5	95*	92*
Samochatova et al.[34]	Russia	Modified BFM 90 with Rituximab	1 (first two blocks)		82

*Results of all risk groups, no documented analysis for subgroups, namely RG3/RG4

CNS involvement is the most important prognostic factor in various studies. Our study represents the treatment outcome of an exclusive group of patients without CNS disease. The comparison of our results with those of the treatment groups with CNS involvement as well as the lack of a control group might be considered as limitations of our study. However, Salzburg et al.[24] reported the outcome of patients with CNS involvement in three consecutive BFM studies and the probability of 5-year EFS was found as 81% in CNS negative stage IV Burkitt's lymphoma/ B cell ALL patients. This might indicate non-inferiority of our modified BFM approach.

There are no randomized clinical trials comparing the efficacy and the toxicity of 1 g/m^2 MTX against 5 g/m^2 MTX, with similar infusion schedules in high-risk lymphoma treatment. As most of the studies submit cumulative therapy outcomes as well as toxicities of all groups together, it is difficult to sort and compare the toxicity rates by each risk group among different studies. In the original NHL-BFM 90 protocol results, the incidence of grade III and IV mucositis was found to be approximately 48% after the blocks containing 5 g/m^2 MTX.[4] We observed grade III and IV mucositis in 40% of our patients after chemotherapy blocks. Celkan et al.[16], from our country, reported mucositis as a common side effect of 5 g/m^2 MTX administration, but the incidence was not reported. Grade III and IV hematologic toxicity was seen in all their HR patients but the incidence of febrile neutropenia was lower (40%) in comparison to our study. Karadeniz et al.[17], again from Turkey, did not reveal a difference in toxicity rates between treatment schedules administering 1 g/m^2, 3 g/m^2, and 5 g/m^2 MTX. The mucositis rate was similar to our results. Grade III-IV hematologic toxicity rates and the incidence of febrile neutropenia episodes were 80% and 70%, respectively, similar to the rates observed in our study. The hematologic toxicity profile was not presented in the original NHL BFM 90 protocol but the febrile neutropenia episodes were observed after 37% and 31% of AA and BB courses, respectively.[4] The toxic death rate for B cell lymphomas ranges between 3% and 20% depending on the development status of the country.[4,5,14,21] Treatment-related mortality rate was found to be 9% in our study. Three of our patients died due to infection, one patient died due to sepsis and tumor lysis syndrome. Deceased patients were transferred from underprivileged regions of our country under inappropriate conditions. Their general status was already poor upon arrival (one with severe tumor lysis syndrome, two with infection in the operative bed, one with spinal cord compression with neurogenic bladder, and a urinary catheter). Our cohort consisted of patients treated between 1999 and 2011. Deaths (including the patient who died while in remission immediately after last chemotherapy cycle) were observed early in the study period when our patients were treated in common crowded wards. Besides, inadequate access to both pediatric intensive care units and to appropriate supportive care were major problems associated with increased mortality at that time. In the study of Celkan et al.[16], treatment-related mortality was higher in the 5 gr/m^2 MTX arm whereas another study from our country did not report any toxic death with 1 gr/m^2, 3 gr/m^2 or 5 gr/m^2 MTX.[17] The difference in treatment-related mortality rates between studies might also be attributed to the infrastructure of the medical center, study era, and the patient-related factors.

We submit the treatment results of the HR BL patients without CNS involvement treated with the modified NHL BFM 90 protocol (i.e. 1 gr/m^2 MTX.) Despite the low dose of MTX, objective response was achieved in all our patients. We did not observe CNS disease in long-term follow-up. None of the patients died due to treatment failure. The survival rate achieved in our study seems comparable to that of original BFM-90 protocol. Although serial MTX measurements and MTHFR gene polymorphism status remain essential for safe MTX administration, the encouraging results of our study raise the question of whether

administration of 1 g/m^2 MTX would be adequate for high-risk BL patients without CNS involvement in developing countries without necessary facilities.

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Author contributions

The authors confirm contribution to the paper as follows: study conception and design: SV, DBG; data collection: SV, İÖD; analysis and interpretation of results: DBG, SV, SK, RK; draft manuscript preparation: SV, DBG. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study is approved by our Hospital Ethics Committee (University of Health Sciences, Şisli Hamidiye Etfal Training and Research Hospital Ethics Committee-Number 3003/2020).

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No funding has been secured for the study.

Conflicts of interest

The authors of this report certify that they don't have any relevant financial, personal or professional relationships with other people or organizations that pose a conflict of interest or that could potentially influence or bias the results of the study described in the manuscript.

REFERENCES

1. Minard-Colin V, Brugieres L, Reiter A, et al. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. J Clin Oncol 2015; 27: 2963-2974.
2. Kutluk MT, Yesilipek A. Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Society. Turkish National Pediatric Cancer Registry 2002-2008 (Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Society. 2013 ASCO Annual Meeting, United States. J Clin Oncol 2013; 31(Suppl 15): 10067.
3. Spreafico F, Massimino M, Luksch R, et al. Intensive, very short-term chemotherapy for advanced Burkitt's lymphoma in children. J Clin Oncol 2002; 20: 2783-2788.
4. Reiter A, Schrappe M, Tiemann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: a report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 1999; 94: 3294-3306.
5. Patte C, Auperin A, Michon J, et al; Société Française d'Oncologie Pédiatrique The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001; 97: 3370-3379.
6. Lopez-Lopez E, Martin-Guerrero I, Ballesteros J, Garcia-Orad A. A systematic review and meta-analysis of MTHFR polymorphisms in methotrexate toxicity prediction in pediatric acute lymphoblastic leukemia. Pharmacogenomics J 2013; 13: 498-506.
7. Cohen IJ. Progression of osteosarcoma after high-dose methotrexate: over-rescue by folinic acid. Pediatr Hematol Oncol 2003; 20: 579-581.
8. Skarby TV, Anderson H, Heldrup J, Kanerva JA, Seidel H, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO). High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. Leukemia 2006; 20: 1955-1962.
9. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. Oncologist 2016; 21: 1471-1482.
10. Kebudi R, Ayan I, Vural S, Gorgun O, Tokuc G. İleri evre lenfoblastik dışı lenfomada yüksek doz metotreksat içeren BFM-NHL 90 protokolünün sonuçları. Türk Hematoloji-Onkoloji Dergisi 1997; 7: 121-130.
11. World Health Organization. WHO handbook for reporting results of cancer treatment. World Health Organization, 1979. Available at: https://apps.who.int/iris/handle/10665/37200 (Accessed on May 5, 2021).

12. Woessmann W, Seidemann K, Mann G, et al; BFM Group. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood 2005; 105: 948-958.

13. Muller J, Csoka M, Jakab Z, Ponyi A, Erlaky H, Kovacs G. Treatment of pediatric non-Hodgkin lymphoma in Hungary: 15 years experience with NHL-BFM 90 and 95 protocols. Pediatr Blood Cancer 2008; 50: 633-635.

14. Buckle G, Maranda L, Skiles J, et al. Factors influencing survival among Kenyan children diagnosed with endemic Burkitt lymphoma between 2003 and 2011: a historical cohort study. Int J Cancer 2016; 139: 1231-1240.

15. Stanley CC, Westmoreland KD, Heimlich BJ, et al. Outcomes for paediatric Burkitt lymphoma treated with anthracycline-based therapy in Malawi. Br J Haematol 2016; 173: 705-712.

16. Celkan TT, Baris S, Ozdemir N, et al. Treatment of pediatric Burkitt lymphoma in Turkey. J Pediatr Hematol Oncol 2010; 32: e279-e284.

17. Karadeniz C, Oguz A, Citak EC, et al. Clinical characteristics and treatment results of pediatric B-cell non-Hodgkin lymphoma patients in a single center. Pediatr Hematol Oncol 2007; 24: 417-430.

18. Kebudi R, Zulfikar B, Cakır FB, et al. Non-Hodgkin lymphoma in children: Is 1 g/m2 methotrexate as effective as 5 g/m2 in advanced-stage nonlymphoblastic non-Hodgkin lymphoma? J Clin Oncol 2013; 31(Suppl 15): 10043.

19. Vural S, Kebudi R, Akıcı F, et al. Results of the modified BFM-NHML 90 chemotherapy regimen in children with advanced stage nonlymphoblastic lymphoma. Med Pediatr Oncol 2003; 41: 254.

20. Klumb CE, Schramm MT, De Resende LM, et al. Treatment of children with B-cell non-Hodgkin's lymphoma in developing countries: the experience of a single center in Brazil. J Pediatr Hematol Oncol 2004; 26: 462-468.

21. Moleti ML, Al-Hadad SA, Al-Jadiry MF, et al. Treatment of children with B-cell non-Hodgkin lymphoma in a low-income country. Pediatr Blood Cancer 2011; 56: 560-567.

22. Acquatella G, Insausti CL, Garcia R, et al. Outcome of children with B cell lymphoma in Venezuela with the LMB-89 protocol. Pediatr Blood Cancer 2004; 43: 580-586.

23. Meremikwu MM, Ehiri JE, Nkanga DG, Udoh EE, Ikpatt OF, Alaje EO. Socioeconomic constraints to effective management of Burkitt's lymphoma in south-eastern Nigeria. Trop Med Int Health 2005; 10: 92-98.

24. Salzburg J, Burkhardt B, Zimmermann M, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group Report. J Clin Oncol 2007; 25: 3915-3922.

25. Woessmann W, Seidemann K, Mann G, et al; BFM Group. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood 2005; 105: 948-958.

26. Kavan P, Kabickova E, Gajdos P, et al. Treatment of children and adolescents with non-Hodgkin's lymphoma (results based on the NHL Berlin-Frankfurt-Munster 90 protocols). Cas Lek Cesk 1999; 138: 40-46.

27. Müller J, Csóka M, Jakab Z, Ponyi A, Erlaky H, Kovács G. Treatment of pediatric non-Hodgkin lymphoma in Hungary: 15 years experience with NHL-BFM 90 and 95 protocols. Pediatr Blood Cancer 2008; 50: 633-635.

28. Pillon M, Di Tullio MT, Garaventa A, et al. Long-term results of the first Italian Association of Pediatric Hematology and Oncology protocol for the treatment of pediatric B-cell non-Hodgkin lymphoma (AIEOP LNH92). Cancer 2004; 101: 385-394.

29. Sun XF, Zhen ZJ, Lui DG, et al. Improved treatment outcome in Chinese children and adolescents with Burkitt's lymphoma and large cell lymphoma by using the modified B-non-Hodgkin's lymphoma-Berlin-Frankfurt-Münster-90 protocol. Eur J Haematol 2006; 77: 365-371.

30. Cervio C, Barsotti D, Ibanez J, Paganini H, Sara Felice M, Chantada GL. Early mortality in children with advanced mature B-cell malignancies in a middle-income country. J Pediatr Hematol Oncol 2012; 34: e266-e270.

31. Chantada G, Casak S, Alderete D, Zubizarreta P, Gallo G, Muriel FS. Treatment of B-cell malignancies in children with a modified BFM-NHL 90 protocol in Argentina. Med Pediatr Oncol 2003; 41: 488-490.

32. Márky I, Björk O, Forestier E, et al; Nordic Society of Pediatric Hematology and Oncology. Intensive chemotherapy without radiotherapy gives more than 85% event-free survival for non-Hodgkin lymphoma without central nervous involvement: a 6-year population-based study from the Nordic Society of Pediatric Hematology and Oncology. J Pediatr Hematol Oncol 2004; 26: 555-560.

33. Dokmanovic L, Krstovski N, Vukanic D, et al. Pediatric non-Hodgkin lymphoma: a retrospective 14-year experience with Berlin-Frankfurt-Münster (BFM) protocols from a tertiary care hospital in Serbia. Pediatr Hematol Oncol 2012; 29: 109-118.

34. Samochatova EV, Maschan AA, Shelikhova LN, et al. Therapy of advanced-stage mature B-cell lymphoma and leukemia in children and adolescents with rituximab and reduced intensity induction chemotherapy (B-NHL 2004M protocol): the results of a multicenter study. J Pediatr Hematol Oncol 2014; 36: 395-401.