

RESEARCH ARTICLE

Clinicopathologic and Survival Characteristics of Childhood and Adolescent Non Hodgkin's Lymphoma in Yazd, Iran

Fariba Binesh¹, Ali Akhavan^{2*}, Nasim Behniafard³, Aref Atefi⁴

Abstract

Background: Data regarding childhood and adolescent non Hodgkin lymphomas in Iran are limited. The aim of this study was to assess the epidemiological and histomorphological features and survival of affected patients in our center. **Materials and Methods:** The clinicopathologic features and outcome of 44 children and adolescents with non Hodgkin lymphoma diagnosed during 2004-2012, were investigated retrospectively. The influence of potential prognostic parameters in overall survival was investigated by log-rank test and Cox regression analysis. **Results:** The mean age at presentation was 13.8 ± 6.16 years with a male predilection (M:F=3:1). Malignant lymphoma, not otherwise specified, diffuse large cell lymphoma and Burkitt lymphoma were the three most common histological types observed. The tumors were 36.4% intermediate grade, 27.3% high grade and 34.1% belonged to the malignant lymphoma not otherwise specified group. Immunohistochemistry findings were available in 39 cases. Out of these cases 33 (84.6%) had B cell lineage, 4 (10.25%) T cell lineage and 2 (5.12%) of the cases belonged to miscellaneous group. 3 year and 5 year survivals were 48% and 30% respectively and median survival was 36 months (95% CI=21.7-50.3 months). Overall survival in patients with high grade tumors was 19.5 months, in the intermediate group, 79 months, and for malignant lymphomas not otherwise specified it was 33.6 months (p value=0.000). **Conclusions:** The survival rate for children and adolescents with non Hodgkin lymphomas at our center during 2004-2012 was at a low level.

Keywords: Non hodgkin lymphoma - survival - relapse - prognosis - patient

Asian Pac J Cancer Prev, 15 (4), 1585-1588

Introduction

Lymphomas account for 10-15% of all pediatric malignancies. It is said that they are highly curable with 5 year survival rates of up to 95% for Hodgkin lymphoma and 82% for non-Hodgkin lymphoma (Frew et al., 2013). Non-Hodgkin lymphoma observed in children and adolescents varies depending on age, histology, gender, and race (Percy et al., 1999). The incidence of non-Hodgkin lymphoma is increasing overall, and there is a slight increase in the incidence for those aged 15 to 19 years; however, the incidence of non-Hodgkin lymphoma in children younger than 15 years has remained constant over the past several decades (Shad et al., 1997). Predisposing factors for the development of childhood non-Hodgkin lymphomas include inherited immune deficiency syndromes such as Ataxia Telangiectasia, Wiskott Aldrich Syndrome and x-linked lymphoproliferative disease, acquired immunodeficiency syndromes such as human immunodeficiency virus infection, patients with organ and bone marrow transplant, Epstein Barr virus infection, solvents and pesticide exposure (Shad et al., 1997; Zekri et al., 2013). Some studies revealed that the risk of non-Hodgkin lymphoma is related to paternal exposure to

oxygenated solvent and petrol exhausts (Miligi et al., 2013). Depending on the geographic region being studied, there are important differences in relation to the clinical and epidemiological characteristics of non-Hodgkin lymphomas diagnosed during childhood (Sandlund et al., 1996). Among the prognostic factors of childhood non-Hodgkin lymphoma that have been studied, there is no consensus in the different studies. Now a days, in developed countries, >80% of children with non-Hodgkin lymphoma are cured by intensive, chemotherapy (Frew et al., 2013). However, in developing countries, the limited availability of resources is an obstacle for using these complicated and intensive protocols. As a result, very simple protocols are used, resulting in poor survival rates. There is a dearth of epidemiological studies conducted on the non-Hodgkin lymphoma in our region and this factor induced us to carry out this study, with the intention of describing the clinical and epidemiological characteristics of our non-Hodgkin lymphoma patients, assessing their survival and searching for possible prognostic associations with the variables under analysis. So the aim of this study is to define distinctive clinicopathologic features and treatment results of these lymphomas in a major tertiary care hospital located in central Iran.

¹Department of Pathology, ²Department of Radiotherapy, ³Research and Development Center, ⁴Biotechnology Laboratory, Shahid Sadoughi University of Medical Sciences, Yazd, Iran *For correspondence: ali52akhavan@yahoo.com

Materials and Methods

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences. In this retrospective project, the medical records of cancer patients were reviewed from 2004 to 2012 and the medical charts of all children and adolescents diagnosed with non-Hodgkin's lymphoma and treated in Shahid Sadoughi hospital were retrieved. Shahid Sadoughi hospital is a major tertiary care hospital located in Yazd, one of the metropolises of Iran. The department of pathology in this hospital receives surgical specimens from major parts of the city as well as from the related large geographical areas in the province including many rural locations. Practically a majority of malignant disorders diagnosed in southeastern Iran are referred to Shahid Sadoughi hospital. Although there are drawbacks of this hospital-based study, the data have some epidemiological significance. Variables recorded were the hospital patient registration number, date, name, age, sex, address, topography, morphology, grading, treatment protocol, lab data, bone marrow aspiration results, relapse, immunophenotyping, if available and survival for each subject according to the clinical data provided in their medical charts and patients follow up via phone. Samples lacking information were not included in the study. Acute leukemias were excluded from this study. We pursued the proposal by Krol et al. (2003) who suggested to use a definition of primary extranodal non-Hodgkin lymphoma that includes all patients who present with non-Hodgkin lymphoma that apparently originated at an extranodal site, even in the presence of disseminated disease, as long as the extranodal component was clinically dominant. The diagnosis of lymphoma was based on histology, following the International Working Formulation classification system. Overall survival was calculated from date of diagnosis until death or date of last follow up. Survival data were analyzed using Kaplan-Meier estimates, and multivariate analysis was performed using the Cox regression method. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS.22.

Results

The records of approximately 90,000 patients who referred to Shahid Sadoughi pathology department, Yazd, Iran over an 8-year period were reviewed. The total number of children and adolescents with non-Hodgkin lymphoma was 46, of which 44 samples were included in the study and the rest were excluded due to incomplete clinical data or uncertain diagnoses. The patients ranged in age from 1.5 to 21 years. The mean age of patients was 13.82 ± 6.16 years. There were 33 males (75%) and 11 females (25%) (M: F ratio=3:1). Of the 44 cases, 23 (52.3%) patients had nodal and 21 (47.3%) showed primary extranodal non-Hodgkin lymphoma. The most common site of extranodal involvement was small intestine (13.6%). Histologically 2.3% of the tumors were low grade, 36.4% exhibiting intermediate grade, 27.3%, high grade and 34.1% belonged to the malignant lymphoma not otherwise specified (NOS) group. Immunohistochemistry findings

were available in 39 cases. Due to financial constraints, immunohistochemistry was not used in the remaining patients. In these cases 33 (84.61%) had B cell lineage, 4 (10.25%) had a T cell lineage and 2 (5.12%) of the cases belonged to miscellaneous group. Bone marrow results were available in 26 patients. Bone marrow involvement was evident in 11 (42.30%) of the patients. Lactate dehydrogenase result was available in 33 patients and in 22 (66.66%) of the cases it was >500 IU/ml. Erythrocyte sedimentation rate in 29 (65%) of the cases was high (in males >10 and in females >20). C reactive protein had been measured in 27 patients which in 19 (70.37) of them was positive. 43 patients received treatment. 15 (34.1%) cases, received chemotherapy, and chemo+radiation therapy was applied in 28 (63.6%) of the patients. Relapse was observed in 25% of the patients. Disease in 15.9% of the patients locally recurred and distant metastases had occurred in 9.1%. 3 and 5 year survival were 48% and 30% respectively and median survival was 36 months (Figure 1). The overall survival was longer in male (53.98 vs 30.52 , p value=0.8), patients with B phenotype tumors (56.69 vs 27.00 , p value=0.15), patients who received radiation therapy+chemotherapy (60.23 vs 35.73 , p value=0.15) and cases without bone marrow involvement (57.25 vs 26.23 , p value=0.3), although these differences failed to reach statistical significance. Overall survival in patients with high grade tumors was 19.54, in the intermediate group, 79 months and in malignant lymphoma not otherwise specified group (NOS), it was 33.61 months (p value=0.00). (Figure 2) In patients with

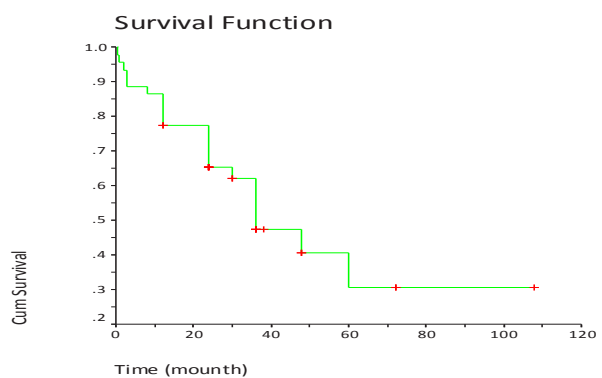


Figure 1. Overall Survival in Children and Adolescents with NHL (3 and 5 year follow up)

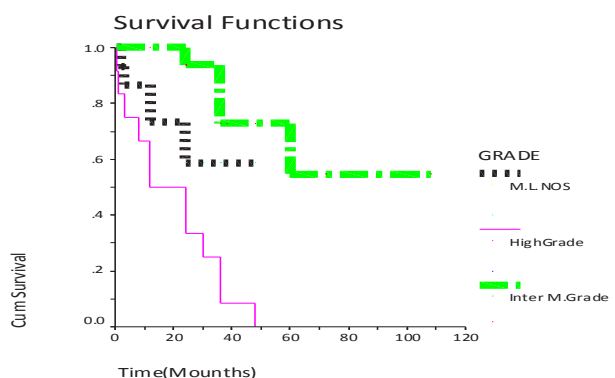


Figure 2. Overall Survival and Histological Grade in Children and Adolescents with NHL (3 and 5 year follow up)

nodal involvement overall survival was 38.22 and overall survival in extra nodal involvement was 60.52 months (p value=0.36). Overall survival in the age group under 15 years was 35.97 months and in the age group over 15 years, it was 59.72 months (p value=0.17). Overall survival in patients with high erythrocyte sedimentation rate level was shorter than patients with normal erythrocyte sedimentation rate (p value=0.05). Overall survival in patients with high level of lactate dehydrogenase was shorter in comparison to patients with normal level of lactate dehydrogenase, although this difference failed to reach statistical significance (p value=0.2). There was no any association between C reactive protein and overall survival (p value=1).

Discussion

This study analyzes epidemiologic characteristic, histopathologic features and treatment results of non Hodgkin lymphomas in a major tertiary care hospital located in central Iran. The death rate for childhood cancer has decreased by more than half over the past 3 decades, from 4.9 (per 100,000) in 1975 to 2.2 in 2008((SEER) Program 2011). The substantial progress for all of the major childhood cancers reflects both improvements in treatment and high levels of participation in clinical trials ((SEER) Program 2011). However, in our province the true incidence, particularly the incidence of different types of non Hodgkin lymphomas, is not known because of under reporting and lack of details. Pediatric Non-Hodgkin lymphomas differ from their adult counterpart in that the low grade follicular lymphomas seen in adults are exceedingly rare in children. Non Hodgkin lymphomas in children and adolescents include Burkitt's lymphoma, diffuse large B cell lymphoma, anaplastic large cell lymphoma and lymphoblastic lymphoma. Depending on the geographic region being studied, there are important differences in relation to the clinical and epidemiological characteristics of non Hodgkin lymphomas diagnosed during childhood (Sandlund et al., 1996). In the presented study the mean age of patients was 13.82±6.16 years. The children admitted to Shahid Sadoughi Hospital seemed to be affected by non-Hodgkin lymphoma at an older age in comparison to other studies (Pedrosa et al., 2007, Yoon et al., 2012, Lervat et al., 2013). With relation to sex, a predominance of male cases was observed, in a proportion of 3:1, which is similar to what is described in the literature (Gutierrez et al., 1992). The reason for this gender predominance is unknown; however, it may reflect a difference in the immune status of males compared with females. In the present study, 2.3% of the tumors were low grade, 36.4% exhibiting intermediate grade, 27.3% high grade and 34.1% belonged to the malignant lymphoma not otherwise specified group (NOS). Many non Hodgkin lymphoma subtypes frequently observed in adults are rarely diagnosed in children and adolescents. In the current study there was only one case of follicular lymphoma. 33 (84.61%) of our cases had B cell lineage, 4 (10.25%) had T cell lineage and 2 (5.12%) of the cases belonged to miscellaneous group. The current study and similar reports from some of the surrounding Middle

East countries as well as the West show a low relative proportion of T-cell lymphomas (Naresh et al., 2004; Economopoulos et al., 2005). It was claimed that non Hodgkin lymphoma, occurring in adolescence was an independent risk factor for a poorer prognosis compared with that occurring in children younger than 15 years of age (Cairo et al., 2003). However it was not true in the presented study and overall survival in the age group over 15 years was longer than the age group younger than 15 years of age, but this difference failed to reach statistical significance (p value=0.17). Results of another study showed that age was not associated as a risk factor for increased treatment failure in either univariate analysis or multivariate analysis (Cairo et al., 2012). Cairo et al. (2012) revealed increased lactate dehydrogenase, and bone marrow positive disease were independent risk factors associated with a poor reduced survival (Cairo et al., 2012). In our study elevated lactate dehydrogenase levels (>500 UI/dl) were observed in 22 (66.66%) cases, high erythrocyte sedimentation rate in 29 (65%) of the cases and C reactive protein was positive in 19 of them. However except for erythrocyte sedimentation rate and histologic grading, none of the analyzed characteristics had a significant association with the probability of survival (p>0.05). The small sample size analyzed in our study could be a possible reason for the lack of overall survival difference between the analyzed variables. Of the 44 cases, 23 (52.3%) patients had nodal and 21 (47.3%) showed primary extra nodal non Hodgkin lymphoma. One explanation for the relatively high incidence of extra nodal non Hodgkin lymphoma in this study (21 out of 44 cases) is increased frequency of gastrointestinal lymphomas in the Middle East. In the current study 3 year and 5 year survival were 48% and 30% respectively and median survival was 36 months which shows that there is a substantial survival difference from childhood and adolescents non Hodgkin lymphoma between Shahid Sadoughi Hospital in Yazd and many developed countries (Fukano et al., 2012; Gerrard et al., 2013; Lee et al., 2013). For example Lee et al showed that the 5-year failure-free survival, event-free survival, and overall survival rates were 86.7±2.9%, 79.1±3.5%, and 84.7±3.1%, respectively in children with non Hodgkin lymphoma (Lee et al., 2013). In another study the estimated event-free survival at 5 years of 76.2±6.6% was reported by Fukano et al., (Fukano et al., 2012). Mary Gerrard revealed that the 5-year overall survival in the 42 children and adolescents with non Hodgkin lymphoma was 73% (95%CI, 56%-84%) (Gerrard et al., 2013).

To explain this difference we should say that in addition to the variation in the incidence, there may be regional and geographical differences in the response to treatment, prognosis and survival for various types of lymphomas. Overall factors known to contribute to racial disparities in mortality include differences in exposure to underlying risk factors access to high-quality and timely diagnosis and treatment, potential long-term or late effects on mortality, and lack of optimal follow-up (Ward et al., 2004). In developing countries, such as Iran, the limited availability of resources is an obstacle for using complicated and intensive protocols. As a result, very simple protocols,

such as the CHOP protocol, were often used to treat children and adolescents with non Hodgkin lymphoma, thus resulting in poor survival rates. In addition childhood non Hodgkin lymphoma is a heterogeneous disease and different biological subtypes require specifically adapted treatment strategies. Children and adolescents with non Hodgkin lymphoma should be referred to medical centers that have a multidisciplinary team of cancer specialists with experience treating the cancers that occur during childhood and adolescence. It should be noted that this study had some limitations: 1-It was a retrospective study. 2- The sample size was small and as a result it could be a possible reason for the lack of overall survival difference between the different analyzed variables. However the results of this analysis will hopefully form the basis of the next studies. Future studies should be developed to evaluate specific therapeutic strategies to overcome these differences in survival between our community and other countries. Increasing survival with non Hodgkin lymphoma is dependent on receiving appropriate cancer therapy. Therefore, efforts to address survival should include improving enrollment in clinical trials as well as increasing access to care.

In conclusion, we evaluated the effect of age, sex, site, histopathology grade, immunohistochemistry markers positivity and some laboratory findings on survival of children and adolescents with non Hodgkin lymphoma in Shahid Sadoughi Hospital in Yazd, Iran. Although except for erythrocyte sedimentation rate and histologic grading, none of the analyzed characteristics had a significant association with the probability of survival, overall survival rate was better in adolescent males with intermediate grade, B phenotype without bone marrow involvement, normal erythrocyte sedimentation rate and lactate dehydrogenase level and patients who were treated with chemotherapy+radiation therapy than those treated with chemotherapy alone.

References

Cairo MS, Sposto R, Gerrard M, et al (2003). Burkitt's and Burkitt-like lymphoma in children and adolescents: A review of the Children's Cancer Group experience. *Br J Haematol*, **120**, 660-70.

Cairo MS, Sposto R, Gerrard M, et al (2012). Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (15 years), are associated with an increased risk of treatment failure in children and adolescents with mature b-cell non-hodgkin's lymphoma: results of the fab lmb 96 study. *J Clin Oncol*, **30**, 387-93.

Economopoulos T, Papageorgiou S, Dimopoulos MA, et al (2005). Non-Hodgkin's lymphomas in Greece according to the WHO classification of lymphoid neoplasms. A retrospective analysis of 810 cases. *Acta Haematol*, **113**, 97-103

Frew JA, Lewis J, Lucraft HH (2013). The management of children with malignant lymphomas. *Clin Oncol*, **25**, 8-11.

Fukano R, Suminoe A, Matsuzaki A, et al (2012). Treatment outcome of non-Hodgkin lymphoma in childhood: KYCCSG NHL-89, 96. *Rinsho Ketsueki*, **53**, 1898-1905

Gerrard M, Waxman I M, Sposto R, et al (2013). Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/

LMB96 mature B-NHL therapy. *Blood*, **121**, 278-85

Gutierrez M I, Bhatia K, Barriga F, et al (1992). Molecular epidemiology of Burkitt's lymphoma from South America: differences in breakpoint location and Epstein-Barr virus association from tumors in other world regions. *Blood*, **79**, 3261-6

Krol A D, le Cessie S, Snijder S, et al (2003). Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. *Ann Oncol*, **14**, 131-9.

Lee S H, Yoo K H, Sung K W, et al (2013). Should children with non-Hodgkin lymphoma be treated with different protocols according to histopathologic subtype? *Pediatr Blood Cancer*, **60**, 1842-7

Lervat C, Auperin A, Patte C, et al (2013). Head and neck presentations of B-NHL and B-AL in children/adolescents: Experience of the LMB89 study. *Pediatr Blood Cancer*, **61**, 473-8.

Miligi L, Benvenuti A, Mattioli S, et al (2013). Risk of childhood leukemia and non-Hodgkin's lymphoma after parental occupational exposure to solvents and other agents: the SETIL Study. *Occup Environ Med*, **70**, 648-55

Naresh KN, Advani S, Adde M, et al (2004). Report of an international network of cancer treatment and research workshop on non-Hodgkin's lymphoma in developing countries. *Blood Cells Mol Dis*, **33**, 330-7.

Pedrosa MF, Pedrosa F, Lins M M, et al (2007). Non-Hodgkin's lymphoma in childhood: clinical and epidemiological characteristics and survival analysis at a single center in Northeast Brazil. *J Pediatr* **83**, 547-54.

Percy CL, Smith MA, Linet M, et al (1999) Lymphomas and reticuloendothelial neoplasms. In: Ries LA, Smith MA, Gurney JG, et al, Eds.: Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, Md: National Cancer Institute, SEER Program. NIH Pub, 99-4649, 35-50.

Sandlund JT, Downing J R, Crist W M (1996). Non-Hodgkin's lymphoma in childhood. *N Engl J Med*, **334**, 1238-48.

Shad A, Magrath I (1997). Non-Hodgkin's lymphoma. *Pediatr Clin North Am*, **44**, 863-90.

Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Mortality-All COD Aggregated with State, Total US (1969-2008) <Katrina/Rita Population Adjustment. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch; 2011. Released September 2011; underlying mortality data provided by National Center for Health Statistics 2011.

Ward E, Jemal A, Cokkinides V, et al (2004). Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*, **54**, 78-93.

Yoon J H, Kang H J, Kim H, et al (2012). Successful treatment of primary central nervous system lymphoma without irradiation in children: single center experience. *J Korean Med Sci*, **27**, 137884.

Zekri AR, Hassan ZK, Bahnassy AA et al (2013). Gene expression profiling of non-Hodgkin lymphomas. *Asian Pac J Cancer Prev*, **14**, 4393-8.