Journal of Pediatric Hematology/Oncology 17(2): 163–166, 1995.

Childhood Non-Hodgkin's Lymphoma in the Five Nordic Countries

A Five-Year Population-Based Study from the Nordic Society of Pediatric Hematology and Oncology

Ildikó Márky, M.D., Kjeld Schmiegelow, M.D., Mikko Perkkiö, M.D., Ólafur G. Jónsson, M.D., Ingebjörg Storm-Mathiesen, M.D., Göran Gustafsson, M.D., Anders Kreuger, M.D., and Fröydis Langmark, M.D.

Purpose: The comparable health-care organizations and common Cancer Registry for childhood malignancies in the five Nordic countries offered an opportunity to conduct an epidemiological study on a reasonable number of childhood non-Hodgkin's lymphoma (NHL) cases collected in a population-based manner.

Material and Methods: All childhood cases (0–14.9 years at diagnosis) reported during the 5-year period of 1985–1989 to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) Cancer Registry for childhood malignancies were reviewed and analyzed according to age, Murphy's stage, gender, site, and survival.

Results: The annual incidence of NHL is 0.7 per 100,000 children in the five Nordic countries, constituting 5% of all childhood malignancies. Age distribution was even; the male/female ratio was 3:1. Age and stage were shown by Cox regression analysis to be independent prognostic factors. Older age and lower stage affected outcome favorably. The stage and site distribution was similar to previous reports. Survival data were in accordance with those expected with modern treatment protocols.

Conclusions: The incidence and relative frequency of NHL in childhood in the five Nordic countries is in agreement with previously reported data, but the even distribution of cases throughout childhood is a new finding. Older age at onset and stage of disease affect outcome favorably, whereas male gender contrary to acute lymphoblastic leukemia was not found to affect outcome.

Key Words: Cancer epidemiology—Childhood non-Hodgkin's lymphoma.

Submitted for publication June 15, 1994. Accepted September 14, 1994.

From the Nordic Society of Pediatric Hematology and Oncology (NOPHO). Participants in this cooperative study were from Denmark (K.S.), Finland (M.P.), Iceland (Ó.G.J.), Norway (F.L., I.S-M.), and Sweden (G.G., A.K., I.M.).

Address correspondence and reprint requests to Dr. Ildikó Márky, University of Göteborg, Department of Pediatrics, East Hospital, S-416 85 Göteborg, Sweden.

The data reported here were submitted by all participants in the study, and some preleminary results were presented as a poster at the 25th Meeting of the International Society of Paediatric Oncology (SIOP), October 5–9, 1993, San Francisco, California, U.S.A.

The types and distribution of malignancies that occur in children differ from those in the adult population. With the unique clinical, biological and genetic features found in pediatric cancers, epidemiological studies conducted in a defined childhood population can contribute to a better understanding of cancer.

Childhood non-Hodgkin's lymphomas (NHLs) occur throughout the world, although their relative frequency varies markedly from country to country (1). The present investigation was prompted by the fact that the comparable health and welfare systems, the fairly homogeneous population, and a common cancer registry for childhood malignancies in the five Nordic countries offered the possibility to analyze a reasonable number of childhood NHL cases collected prospectively in a population-based manner.

MATERIAL AND METHODS

National cancer registries were established in the five Nordic countries during the 1940s and 1950s: in Denmark in 1943, in Norway in 1951, in Finland in 1953, in Iceland in 1955, and in Sweden in 1958. In addition to these registries, in 1982, through the work of the Nordic Society of Pediatric Hematology and Oncology (NOPHO) a central Cancer Registry for Solid Tumors in Childhood, common for all five Nordic countries, was also established. This registry is directed by the head (F.L.) of the Norwegian Cancer Registry. Data from the five countries are reported annually and coded in the registry.

The NOPHO collects data on the patient's age at diagnosis, gender, congenital abnormalities, hereditary diseases, previous health, immunophenotype, site, stage,

and outcome of the disease. Data are also collected on the parents' ages and ethnic backgrounds.

The time period chosen for the present investigation was the 5-year period of 1985–1989 because data from the earlier period were judged to be incomplete. The data were cross-checked with the national cancer registries and with the NOPHO Registry for Leukemias in Childhood to rule out double registration or missing patients with NHL registered as acute lymphoblastic leukemia (ALL). No such cases were found. All registration forms were reviewed by two of the authors (F.L. and I.M.). If necessary, staging was changed to Murphy's classification (2). All patients were treated with modern NHL protocols (BFM, LSA2L2, WCI 7704, COMP, Ziegler, and CCG 552), but because treatment was not uniform during the investigation period, analysis of data according to treatment was not conducted. Because data on immunophenotype were missing in 25% (39 of 156) of the cases, only crude data were included. Analysis of phenotype by age, site, gender, and survival were not conducted. All patients were followed by scheduled examinations at the referring hospital or at a child cancer unit for at least 5 years after diagnosis.

The statistical methods used were Cox's multiple regression analysis and life-table analysis (3,4).

During these 5 years, 156 children who were 0–14.9 years of age at the time of the NHL diagnosis were registered from four of the Nordic countries. Iceland registered no children with NHL during this time period.

RESULTS

The total population in the five Nordic countries is 22 million, of which 4.2 million were children <15 years of age, which gives an annual incidence of NHL of 0.7 per 100,000 children, representing 5% of all childhood malignancies during the investigation period. Eighty- eight percent of the children were of Nordic ethnic background, 1% had other caucasian backgrounds, 3% were Asian, and 2% other; in 6% the ethnic background was not reported. The male/female ratio was 3:1.

Of the 156 children with NHL, 14% had stage I, 19% stage II, 51% stage III and 16% stage IV disease. Thirty-nine percent of the patients were 0–<7 years of age, 37% 7–<12, and 24% ≥12 at diagnosis (Table 1). Thirty-five percent of the patients had abdominal, 27% thoracic, and 38% other sites as location of the disease (Table 1).

The age distribution was uniform, with the exception of the youngest (<3 years) and oldest (>13.9 years) age groups, in which a smaller number of cases was noted (Fig. 1). Thirty-nine percent of the patients were <7 years of age at diagnosis. No difference in the distribution of stages and sites was observed among the different age groups.

The male/female ratio was 3:1, with considerable variation in different age groups (Fig. 1). The percentage of females was highest in stage I and lowest in stage IV patients, but the difference was not statistically significant (Table 1).

Sixty-seven patients had B-NHL, 45 T-NHL, and five Ki-1–positive NHL. In 39 patients the immunophenotype was not stated. Seventy-eight percent of the T-NHLs were thoracic, whereas 52% of the B-NHLs were abdominal. No B-NHL was localized in the thorax.

Three of the 156 patients were reported to have had previous disease: one was treated for rheumatoid arthri-

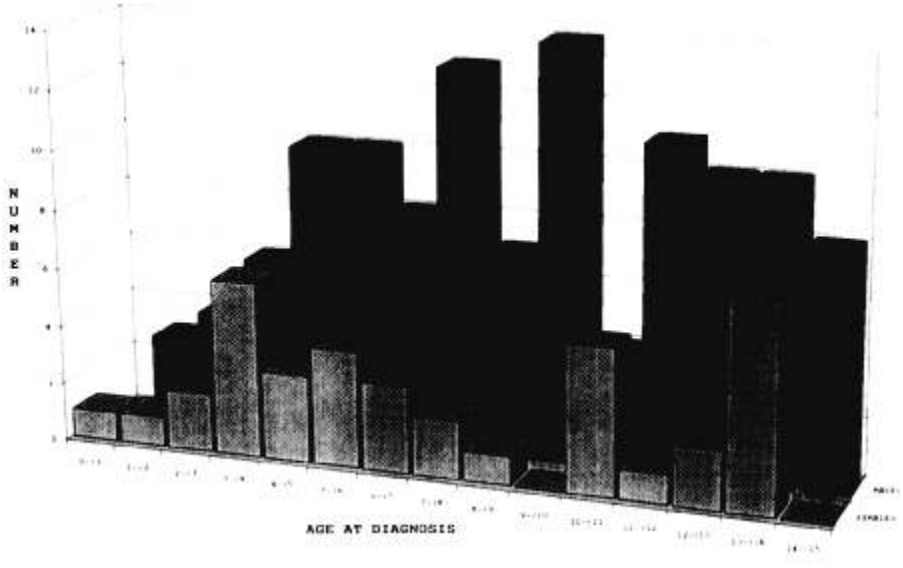

FIG. 1. Distribution of gender by age of the 156 Nordic children with NHL.

TABLE 1. *The distribution of stage, gender, age and site of NHL in 156 Nordic children*

Stage	I	II	III	IV	Total
n	21	30	80	25	156
%	13,5	19,2	51.3	16	100
Gender					
F	7(33%)	7(23%)	19(24%)	5(20%)	38(24%)
m	14(67%)	23(77%)	61(76%)	20(80%)	118 (76%)
Age (years)					
<2	1	1	2	1	5(3%)
2–<7	10	8	30	8	56(36%)
7–<12	4	12	28	20	58(37%)
=>12	6	9	20	2	37(24%)
Site					
Abdomen	0	9	37	8	54 (35%)
Thorax	0	0	34	8	42(27%)
Other sites	21	21	9	9	60(38%)
Country					
Denmark	3	7	14	5	29
Iceland	0	0	0	0	0
Finland	6	4	17	3	30
Norway	3	6	17	5	31
Sweden	9	13	32	12	66

tis with corticosteroids, one was treated for Ewing's sarcoma with combination chemotherapy and irradiation, and one was diagnosed with "lymphocytoma unspecified" (not AML), for which the patient did not receive treatment.

Three patients were reported to have malformations and eight had unspecified chronic disease; information was lacking regarding these data on 10 of the 156 patients. The mean age of the mothers was 26.9 years and of the fathers 29.9 years.

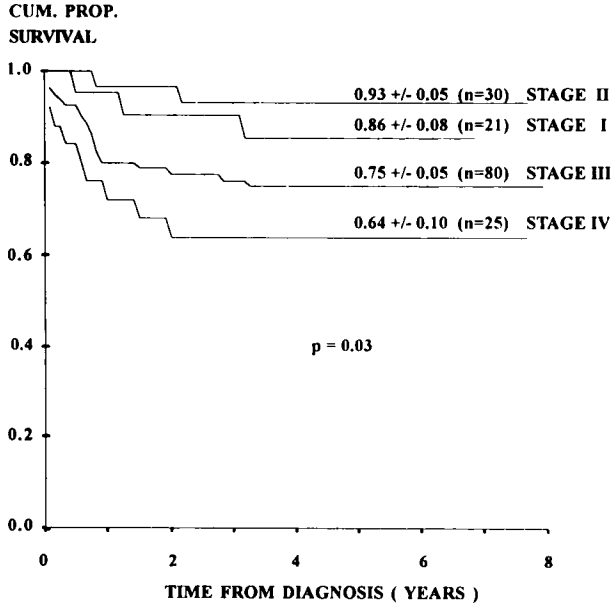

FIG. 2. Overall survival by stage of the 156 Nordic children with NHL.

The overall survival for the whole group was 78%. Life-table analysis according to stage and age are shown in Figs. 2 and 3. The overall survival for stage I and stage II patients was 86% and 93%, respectively, for stage III patients 75%, and for stage IV 64%. Survival by age was significantly ($p = 0.03$) better for patients >12 years of age and worst for children <2 years of age at the time of the diagnosis. Site and gender did not affect survival. Survival was 76% for thoracic, 72% for abdominal, and 85% for other sites. Survival was 82% for females and 77% for males.

Cox's regression analysis with reference to age at diagnosis, gender, stage, and site showed significance for stage ($p = 0.025$) and age ($p = 0.035$).

DISCUSSION

Because our data were collected prospectively, reported and updated annually, and cross- checked with each country's cancer registry and the Nordic Leukemia Register for Children, we have reason to believe that our findings represent the true characteristics of NHL in children in the five Nordic countries.

Our annual incidence of 0.7 cases per 100,000 children is the same as reported by SEER (5) and by the National Registry of Childhood Tumours in England, Scotland, and Wales (6). The relative frequency of 5%—which for NHL is known to vary markedly from country to country (1)—is in accordance with data from the National Cancer Institute (7). The fact that our population was composed of 89% white children supports the view that this is the true relative frequency of NHL in white children in Western industrialized nations.

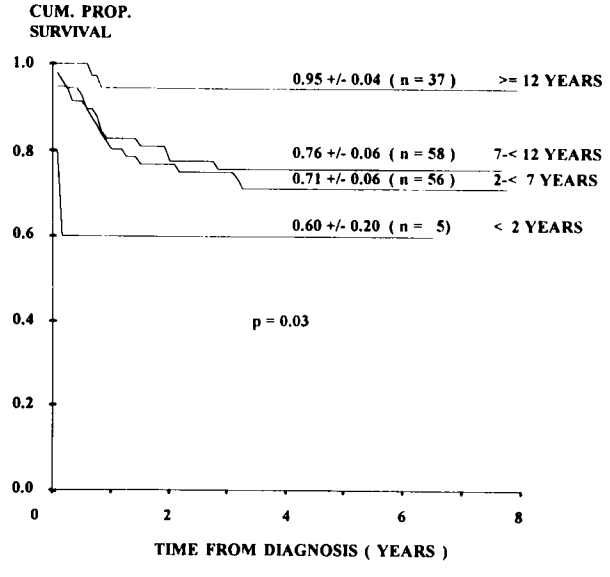

FIG. 3. Overall survival by age of the 156 Nordic children with NHL.

In contrast to previous studies (1,8,9), we found an even distribution of cases throughout childhood with no peak incidence. Thirty-nine percent of the children were <7 years of age. It is worth pointing out that a similarly conducted NOPHO study on children with AML also found a different age distribution from others (10). However, the distribution of sites and stages was in agreement with earlier published studies, as was the male/female ratio of 3:1. Few patients in our study had previous diseases, including cancer.

Survival results were as expected with modern treatment (11). Age and stage affected outcome of the disease, older age and lower stage being favorable prognostic factors. One explanation for the better outcome in stage II than stage I could be that the lowest stages were undertreated; however, the number of cases in each stage is small, and the differences could represent only random fluctuation.

Because NHL is known to share some biological features with acute lymphoblastic leukemia, it is important to point out the differences in our study. Contrary to acute lymphoblastic leukemia, the NHL patients lacked the familiar age of onset peak of acute lymphoblastic leukemia, there was a pronounced male/female preponderance, older age at diagnosis affected outcome favorably, and male gender did not influence survival.

With improvements in reporting on phenotypes, we hope to be able to analyze their distribution in Nordic children with NHL in the future.

REFERENCES

1. West E. Childhood cancer mortality: international comparison 1955–1974. *World Health Stat Q* 1984;37:98.
2. Murphy SB. Classification, staging and end results of treatment in childhood non-Hodgkin's lymphoma: dissimilarities from lymphomas in adults. *Semin Oncol* 1980;7:331–9.
3. Kaplan E, Meier P. Non-parametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:457–31.
4. Cox DR. Regression models and life-tables. *J R Stat Soc* 1972;34:187–220.
5. Ries LA, Hankey BF, Miller BA, et al., eds. *Cancer Statistics Review* 1973–88. NH Publication *No 91-2789*. Bethesda, MD: National Cancer Institute, 1991.
6. Stiller CA. Aetiology and epidemiology. In: Plowman PN, Pinkelton CR, eds. *Paediatric oncology. Clinical practice and controversies*. London: Chapman and Hall Medical, 1992.
7. Young JL, Ries LG, Silverberg E, et al. Cancer survival and mortality for children younger than 14 years. *Cancer* 1986;58:598–602.
8. Patte C. Childhood non-Hodgkin's lymphoma. In: Pizzo PA, Poplack DG, eds. *Paediatric oncology. Principles and practice of pediatric oncology*. 2nd ed. Philadelphia, PA: JB Lippincott, 1993.
9. Crist WM, Kelly DR, Ragabs AH, et al: Predictive ability of Lukes-Collins classification for immunologic phenotypes of childhood non-Hodgkin's lymphoma: an institutional series and literature review. *Cancer* 1981;48:2070–5.
10. Slördal SH, Gustafsson G, Jonmundsson G, et al. Down's syndrome (DS) and acute myelogenous leukemia (AML). A population based study in the five Nordic countries. *Med Pediatr Oncol* 1992;20:373.
11. Murphy SB, Magrath IT. Workshop on pediatric lymphomas: current results and prospects. *Ann Oncol* 1991;2(suppl):219–23.