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Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents

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Haematologica 2016
Volume 101(12):1581-1591

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Received: March 30, 2016.

Accepted: August 9, 2016.

Pre-published: August 11, 2016.

doi:10.3324/haematol.2016.147116

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/101/12/1581

ABSTRACT

Children and adolescents with pre-existing conditions such as DNA repair defects or other primary immunodeficiencies have an increased risk of non-Hodgkin lymphoma. However, large-scale data on patients with non-Hodgkin lymphoma and their entire spectrum of pre-existing conditions are scarce. A retrospective multinational study was conducted by means of questionnaires sent out to the national study groups or centers, by the two largest consortia in childhood non-Hodgkin lymphoma, the European Intergroup for Childhood non-Hodgkin Lymphoma, and the international Berlin-Frankfurt-Münster Study Group. The study identified 213 patients with non-Hodgkin lymphoma and a pre-existing condition. Four subcategories were established: a) cancer predisposition syndromes (n=124, 58%); b) primary immunodeficiencies not further specified (n=27, 13%); c) genetic diseases with no increased cancer risk (n=40, 19%); and d) non-classifiable conditions (n=22, 10%). Seventy-nine of 124 (64%) cancer predispositions were reported in groups with more than 20 patients: ataxia telangiectasia (n=32), Nijmegen breakage syndrome (n=26), constitutional mis-

match repair deficiency (n=21). For the 151 patients with a known cancer risk, 5-year event-free survival and overall survival rates were 40%±4% and 51%±4%, respectively. Five-year cumulative incidences of progression/relapse and treatment-related death as a first event were 22%±4% and 24%±4%, respectively. Ten-year incidence of second malignancy was 24%±5% and 7-year overall survival of the 21 patients with a second malignancy was 41%±11%. Patients with non-Hodgkin lymphoma and pre-existing conditions have an inferior survival rate with a large proportion of therapy-related deaths compared to patients with non-Hodgkin lymphoma and no pre-existing conditions. They may require special vigilance when receiving standard or modified/reduced-intensity chemotherapy or when undergoing allogeneic stem cell transplantation.

Introduction

Although causes of childhood cancer remain largely unknown, recent studies have shown germline genetic variants in a variety of genes, and, in particular, mutations in cancer predisposition genes, to be associated with the occurrence of lymphoid malignant diseases such as acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL).[1-4] Two studies found that 8.5%-10% of children and adolescents with cancer have pathogenetic genomic alterations in cancer predisposition genes, suggesting that family history alone is not a reliable marker for the likelihood of a pre-existing cancer predisposition in any patient with a newly diagnosed malignancy.[2-4]

A wide spectrum of clinically evident and/or molecularly defined pre-existing conditions carries an increased risk of cancer development, although the reasons for the specific predisposition for lymphoid malignancies such as leukemia and lymphoma have not been fully clarified.[5-19] Primary immunodeficiencies (PID) such as DNA repair defects (Nijmegen breakage syndrome, Ataxia telangiectasia, Bloom syndrome or constitutional mismatch repair deficiency), severe combined immunodeficiencies (SCID), common variable immunodeficiencies (CVID), and immune-osseous dysplasias (Di George syndrome or cartilage hair hypoplasia) have an extraordinary risk of developing leukemia and lymphoma.[5-17,20,21] Although these patients seem to have an inferior prognosis and an increased risk of treatment-related toxicity and death compared to patients with lymphoid malignancies without a PID, curative therapies including allogeneic stem cell transplantation (allo-SCT) have been repeatedly reported.[5,6,10,11,15,16,22]

Systematic data on the spectrum of common and rare pre-existing conditions associated with NHL in children and adolescents are scarce with respect to the type of the pre-existing conditions and the clinical characteristics and outcome of the associated NHL subtypes. Thus, the two largest childhood NHL consortia, the European Intergroup for Childhood NHL (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Study Group (SG), designed a retrospective multinational study to collect data on unselected types of pre-existing conditions among children and adolescents with NHL. The study was carried out in full recognition of the limitations imposed by the fact that such a large retrospective study may lack complete accuracy and could, therefore, make unequivocal interpretation difficult.

Methods

Between April 2014 and December 2015 we performed an international survey of children and adolescents aged 0-19 years presenting with pre-existing conditions and NHL. Pre-existing conditions were defined as any proven or suspected inherited medical condition. As a prerequisite, the analysis only included patients with nationally centrally-reviewed histopathology of the NHL subtype. Patients diagnosed between 1984 and 2015 (1984-2000: n=45; 2000-2015: n=168) were retrieved from 21 EICNHL and/or i-BFM Study Group members. The survey included questions about demographics and disease [pre-existing condition, NHL subtype, age, sex, stage of disease and pre-therapeutic lactate dehydrogenase (LDH) level], treatment (chemotherapy, radiotherapy and SCT), and outcome (date of progression/relapse, secondary malignancy and death). The letter of invitation and the complete questionnaire are provided at the beginning of the *Online Supplementary Appendix* and in *Online Supplementary Table S1*, respectively.

By 1st January 2016, 213 patients with NHL and a pre-existing condition had been identified. Diagnosis of the NHL subtype was based on the contemporary application of morphological and immunophenotypic criteria.[23-25] Staging procedures are described in detail elsewhere.[26] Patients were included in national studies or registries. In some of these, patients were treated according to treatment guidelines for children with PID/chromosomal breakage syndromes. Of the 213 patients, 174 (82%) were treated according to protocols of the EICNHL, NHL-BFM SG, AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica), UKCCSG (United Kingdom Children's Cancer SG), SFOP (Société Française d'Oncologie Pédiatrique), EORTC (European Organisation for Research and Treatment of Cancer), COG (Children's Oncology Group), and JPLSG (Japanese Pediatric Leukemia/Lymphoma SG).[27-42] The remaining 39 patients (18%) received CHOP±rituximab, COP±rituximab, rituximab only, or miscellaneous treatments. The survey asked for information about dose reductions, suspension of chemotherapy elements or single drugs, and individualized therapy approaches. Unfortunately, these were not reported in all patients making it impossible to assess whether modifications of therapy influenced therapy-related toxicity and mortality, response and outcome.

All patients were treated after informed consent from the patient, or the patient's parents or legal guardian. Treatment studies were conducted according to the Declaration of Helsinki and approved by the respective ethics committees of the participating bodies.

Statistical analysis

Event-free survival (EFS) and overall survival (OS) were ana-

lyzed by the Kaplan-Meier method and compared by the log-rank test. Event-free survival was defined as the time from diagnosis of NHL to the first adverse event (first relapse, progression, secondary malignancy, death from any cause) or date of last follow up. Overall survival was defined as the time from diagnosis of NHL to death from any cause or date of last follow up. Cumulative incidence functions for competing events were constructed by the method of Kalbfleisch and Prentice and were compared with the Gray's test. Cumulative incidences of relapse/progression (CIR) were estimated taking into account death without relapse/progression and secondary malignancies (SML) as competing events. Cumulative incidence of treatment-related death (CID) as a first event was estimated taking into account relapse/progression and SMLs as competing events. Results are shown by percentages and include standard errors. Median follow up was calculated for surviving patients. Statistical analysis was performed using the SAS statistical program (SAS-PC, v.9.3; SAS Institute, Cary, NC, USA).

Results

Four subgroups were identified (Table 1): a) known cancer predisposition syndromes (n=124, 58%); b) PIDs not further specified (defined as having no definite genetic characterization; n=27, 13%); c) genetic diseases not known to be associated with an increased cancer risk (n=40, 19%); and d) non-classifiable pre-existing conditions (n=22, 10%), including pre-existing conditions of multifactorial etiology (n=7), organ malformations (n=5), and syndromes not further specified (n=10).

For the entire group of 213 patients, 5-year EFS and OS rates were 45%±4% and 54%±4%, respectively (*Online Supplementary Figure S1A* and *B*) after a median follow up of 4.95 years (range 0.33-18.80 years). Five-year CIR and CID were 26%±3% and 19%±3%, respectively (*Online Supplementary Figure S1C and D*). When restricting out-

Table 1. Four categories of pre-existing conditions in 213 patients with non-Hodgkin lymphoma.

Type of pre-existing condition	Condition (mode of transmission, incidence *per* live birth)	N. patients
All patients		213
Cancer predisposition syndrome (n>1 patient)		124
	Ataxia telangiectasia (AR, 1:4000)	32 (26%)
	Nijmegen breakage syndrome (AR, 1:100,000)	26 (21%)
	Constitutional mismatch repair disease (AR and AD*, n.a.)	21 (17%)
	X-linked lymphoproliferative syndrome (recessive, 1:1,000,000)	11 (9%)
	Wiskott-Aldrich syndrome (X-linked recessive, 1:100,000-250,000)	7 (6%)
	Chromosomal breakage syndrome n. f. sp. (AR, n.a.)	3 (2.5%)
	Down syndrome (trisomy 21, 1:500-800)	3 (2.5%)
	Neurofibromatosis type 1 (AD, 1:2500-3300)	3 (2.5%)
	Cartilage hair syndrome (AR, 1:18.000-23,000)	2 (1.5%)
	Hyper-IgM syndrome (AR, 0.2:100,000)	2 (1.5%)
	Hyper-IgE syndrome (AR, 1:1,000,000)	2 (1.5%)
	Others (each in 1 patient)	12 (10%)
Immunodeficiencies n.f.sp.		27
	Primary immunodeficiency n.f.sp.	20 (74%)
	Common variable immunodeficiency	7 (26%)
Genetic disease (n>1 patient)		40
	G6PD deficiency (X-linked recessive, incidence region-dependent)	4 (10%)
	Cystic fibrosis (AR, 1:2000)	2 (5%)
	Hemophilia A (X-linked recessive, 1:5000)	2 (5%)
	α-1-antitrypsin deficiency (AR, 1:2000-5000)	2 (5%)
	Williams-Beuren syndrome (del 7q11.23, 1:7500-20,000)	2 (5%)
	Prader-Labhart-Willi syndrome (15p aberrations, 1:10,000-15,000)	2 (5%)
	Others (each in 1 patient)	26 (65%)
Non-classifiable conditions		22
Multifactorial disease		7
	Familial myoclonic epilepsy	2 (29%)
	Autism	2 (29%)
	Gilles de la Tourette syndrome	1 (14%)
	Congenital hearing loss	1 (14%)
	Autoimmune enteropathy	1 (14%)
Organ malformation		5
	Congenital heart disease	1 (20%)
	Malformation of the CNS	2 (40%)
	Kidney agenesis	1 (20%)
	Skeletal malformation	1 (20%)
Syndromes n.f.sp.		10
	Complex developmental delay	8 (80%)
	Others (each in 1 patient)	2 (20%)

*N.: number; n.a.: not available; AR: autosomal recessive inheritance; AD: autosomal dominant inheritance; n.f.sp.: not further specified; G6PD: glucose-6-phopsphate dehydrogenase; CNS: central nervous system. *Lynch syndrome.*

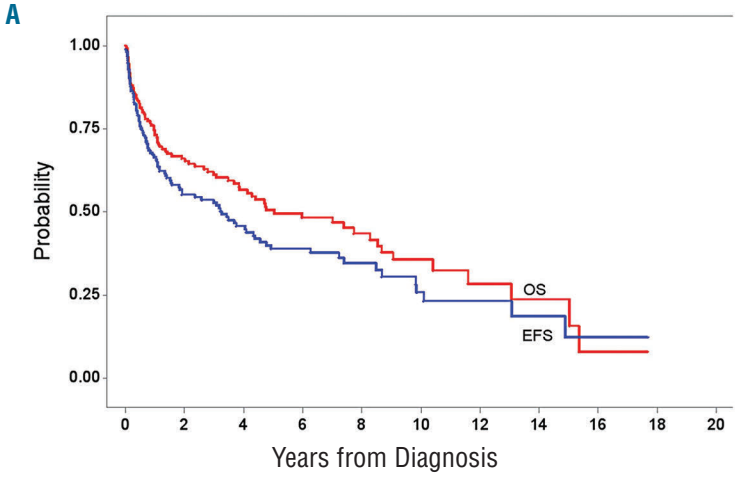
come analysis to the 151 patients with cancer predisposition syndromes and PIDs not further specified, 5-year EFS and OS rates were 40%±4% and 51%±4% (Figure 1A and B) and 5-year CIR and CID were 22%±4% and 24%±4%, respectively (Figure 1C and D) after a median follow up of 4.91 years (range 0.33-17.67 years).

Known cancer predisposition syndromes

Among the 124 patients with a cancer predisposition syndrome, 112 (90%) diagnoses were reported in more than 1 patient: ataxia telangiectasia (AT, n=32), Nijmegen breakage syndrome (NBS, n=26), constitutional mismatch repair deficiency (CMMRD, n=21), X-linked lymphoproliferative disease (XLP, n=11), Wiskott-Aldrich syndrome (WAS, n=7), Down syndrome (DS, n=3), chromosomal breakage syndromes not further specified (n=3), neurofibromatosis type 1 (NF1, n=3), and 2 patients each with cartilage hair syndrome, hyper-IgM syndrome, and hyper-IgE syndrome. Patients' characteristics and outcomes are shown in Table 2 (diagnoses >2 patients, n=106) and *Online Supplementary Table S2* (diagnoses <3 patients, n=18), respectively.

Male-to-female ratio was 2:1 and median age was 7.98 years (range 0.19-18.20 years). The distribution of histological subtypes was: mature B-cell NHL (n=75, 60%), lymphoblastic lymphoma [T-LBL, n=27, 22%, and B-cell precursor (BCP)-LBL, n=3, 2%], peripheral T-cell lymphoma (PTCL, n=9, 7%), anaplastic large cell lymphoma (ALCL, n=6, 5%), and other NHL subtypes (n=4, 3%).

Twenty-eight of 124 patients (23%) suffered from progression/relapse and 21 (17%) from an SML. In addition, one patient with XLP developed a secondary aplastic anemia and one patient with chromosomal breakage syndrome not further specified developed a hemophagocytic lymphohistiocytosis. Sixty-seven of 124 patients (54%) died, 18 (27%) from primary NHL, 14 (21%) from SML, 30 (45%) from therapy-related toxicity (including 3 SCT-related deaths); information on the cause of death was not available for 3 patients (4%). Two patients (3%) died from AT-related complications.



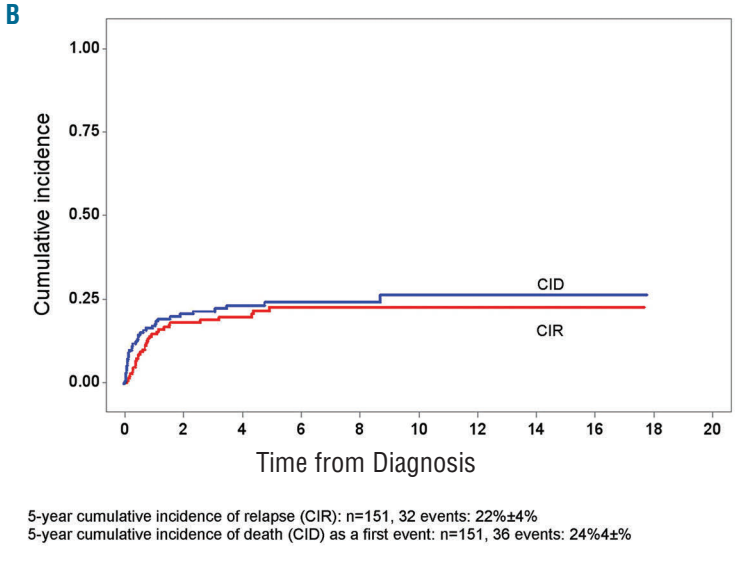


Figure 1. Five-year event-free and overall survival rates (A) and 5-year cumulative incidence rates of relapse and treatment-related death (B) of the 151 patients with cancer predisposition syndromes (n=124) and primary immunodeficiencies (PIDs) not further specified (n=27).

Twenty-two of 124 patients (18%) underwent allo-SCT. Of the 16 patients transplanted in first complete remission (CR), 13 (81%) have not yet experienced any event while 3 (19%) died from toxicity. Three of the remaining 6 transplanted patients were transplanted for relapsed disease. Among these 3 there were 2 deaths; one for aplastic anemia (alive) and one for hemophagocytic lymphohistiocytosis (dead). For the 1 surviving patient, the time point of SCT was not available. After a median follow up of 5.46 years (range 0.33-17.67 years), 5-year EFS and OS rates were 40%±5% and 53%±5%, respectively (Figure 2A and B). Five-year CIR and CID were 24%±4% and 21%±4%, respectively (Figure 3A and B).

Primary immunodeficiencies not further specified

Among the 27 patients with a PID not further specified, there were 7 (26%) patients with a common variable immunodeficiency (CVID) and 20 (74%) with an immunodeficiency without a definite genetic characterization as reported by the treating physicians. Characteristics and outcomes of these patients are shown in Table 3.

Male-to-female ratio was 1.1:1 and median age was 5.83 years (range 0.70-17.84 years). The distribution of histological subtypes was: mature B-cell NHL (n=21, 78%), lymphoblastic lymphoma (T-LBL, n=1, 4%), PTCL (n=3, 11%), and ALCL (n=2, 7%). Four of 27 patients (15%) experienced progression/relapse. However, 14 (52%)

Table 2. Clinical and laboratory characteristics and outcome of non-Hodgkin lymphoma patients in 8 categories of cancer predisposition syndromes (n>2 patients).

	AT	NBS	CMMRD	XLP	WAS	DS	NF1	CBS n.f.sp.
N. of patients	32	26	21	11	7	3	3	3
Sex								
Male	21 (66%)	15 (58%)	15 (71%)	11 (100%)	7	2	2	2
Female	11 (34%)	11 (42%)	6 (29%)	0	0	1	1	1
Age (years) at dg.								
Median	9.88	9.95	7.1	6.04	7.52	7.64	4.47	15.57
Range	3.30-17.85	2.65-18.20	2.87-17.97	2.38-16.42	0.53-17.24	3.38-14.45	3.38-10.33	12.01-15.89
Histology								
Mature B-NHL	27 (84%)	12 (46%)	3 (14%)	11 (100%)	5	1	1	2
Burkitt lymphoma	6	1	1	5	1	0	1	0
DLBCL	17	8	2	5	2	1	0	0
PMLBCL	0	0	0	0	1	0	0	0
B-cell NHL n.f.sp.	2	2	0	1	1	0	0	2
others	2	1	0	0	0	0	0	0
T-LBL	0	5 (19%)	17 (81%)	0	0	0	2	0
BCP-LBL	2 (6%)	0	1 (5%)	0	0	0	0	0
ALCL	2 (6%)	1 (4%)	0	0	1	0	0	1
PTCL	1 (3%)	6 (23%)	0	0	0	2	0	0
Others	0	2 (8%)	0	0	1	0	0	0
Stage of disease								
I	4 (13%)	1 (4%)	0	0	1	0	0	0
II	10 (31%)	0	0	2 (18%)	1	0	0	1
III	12 (38%)	16 (62%)	20 (95%)	3 (27%)	4	2	3	2
IV	4 (13%)	8 (31%)	1 (5%)	2 (18%)	0	0	0	0
Not available	2 (6%)	1 (4%)	0	4 (36%)	1	1	0	0
LDH								
≥500 U/l	6 (19%)	12 (46%)	5 (24%)	1 (9%)	0	1	0	1
<500 U/l	21 (66%)	13 (50%)	2 (10%)	6 (55%)	4	1	3	1
Not available	5 (16%)	1 (4%)	14 (66%)	4 (36%)	3	1	0	1
Relapse/progression	5 (16%)	10 (38%)	7 (33%)	0	0	2	0	0
Second malignancy	3 (9%)	4 (15%)	11 (52%)	1 (9%)	1	0	1	0
Death	24 (75%)	16 (62%)	15 (71%)	1 (9%)	2	1	1	1
Disease-related	3	7	6	0	0	1	0	0
Therapy-related	16	6	0	1	1	0	0	1
SML-related	2	2	9	0	0	0	1	0
Other/not available	3*	1*	0	0	1	0	0	0
In CR	8 (25%)	10 (38%)	6 (29%)	10 (91%)	5	2	2	2
Follow-up (years)								
Median	4.92	2.92	5.63	4.64	5.98	1.19	6.78	6.95
Range	1.75-7.21	0.51-10.85	1.42-10.23	1.87-15	4.43-10.83	0.88-1.5	5.46-8.1	5.77-8.12

*AT: ataxia telangiectasia; NBS: Nijmegen breakage syndrome; CMMRD: constitutional mismatch repair disease; XLP: X-linked lymphoproliferative disease; WAS: Wiskott-Aldrich syndrome; DS: Down syndrome; NF1: neurofibromatosis type 1; CBS n.f.sp.: chromosomal breakage syndrome not further specified; N.: number; dg.: diagnosis; B-NHL: B-cell non-Hodgkin lymphoma; T-LBL: T-cell lymphoblastic lymphoma; BCP-LBL: B-cell precursor lymphoblastic lymphoma; ALCL: anaplastic large cell lymphoma; PTCL: peripheral T-cell lymphoma; DLBCL: diffuse large B-cell lymphoma; PMLBCL: primary mediastinal large B-cell lymphoma; n. f. sp.: not further specified; LDH: lactate dehydrogenase; SML: secondary malignancy; CR: complete remission. *Two of 3 patients with AT and one patient with NBS died from complications of the underlying DNA repair defect.*

patients died: 2 (14%) from the underlying NHL, 11 (79%) from therapy-related toxicity (including 2 SCT-related deaths), and 1 (7%) patient from complications of the underlying CVID. Eleven of 27 patients (41%) underwent allo-SCT. Ten were transplanted in first CR with only 2 deaths (25%) from toxicity. For 1 patient who died from relapsed disease, the time point of SCT was not available. After a median follow up of 3.28 years (range 0.85-14.56 years), 5-year EFS and OS rates were 37%±11% and 43%±11%, respectively (Figure 2A and B). Five-year CIR and CID were 18%±9% and 41%±11%, respectively (Figure 3A and B).

Genetic diseases not known to be associated with an increased cancer risk

Among the 40 patients within this group, 14 (35%) diagnoses were reported in more than 1 patient: glucose-6-phosphate dehydrogenase deficiency (G6PD, n=4), hemophilia A (n=2), cystic fibrosis (n=2), α-1 antitrypsin deficiency (n=2), Prader-Labhart-Willi syndrome (n=2), and Williams-Beuren syndrome (n=2). Characteristics and outcomes are shown in *Online Supplementary Table S3* (diagnosed in >2 patients, n=4) and *Online Supplementary Table S4* (diagnosed in <3 patients, n=36), respectively.

Male-to-female ratio was 1.8:1 and median age was 10.02 years (range 1.05-18.70 years). The distribution of histological subtypes was: mature B-cell NHL (n=26, 65%), lymphoblastic lymphoma (T-LBL, n=3, 7.5% and BCP-LBL, n=2, 5%), PTCL (n=3, 7.5%), ALCL (n=5, 12.5%), and other NHL subtypes (n=1, 2.5%).

Twelve of 40 patients (30%) experienced progression/relapse and 10 (25%) died, of whom 5 (50%) from the underlying NHL and 5 (50%) from therapy-related toxicity (no SCT-related death). Two of 40 patients (5%) underwent allo-SCT. The patient with CTP synthase 1 deficiency transplanted in first remission is alive. The remaining patient with Kartagener syndrome transplanted for relapsed T-LBL died from progression. After a median follow up of 4.96 years (range 0.39-18.80 years), 5-year EFS and OS rates were 61%±8% and 72%±8%, respectively (Figure 2A and B). Five-year CIR and CID were 35%±10% and 9%±7%, respectively (Figure 3A and B).

Non-classifiable pre-existing conditions

Out of the 22 patients with non-classifiable pre-existing conditions, 7 had pre-existing conditions of idiopathic or multifactorial etiology (32%), 5 pre-existing organ malformations (23%), and 10 patients were reported with symptoms and/or a developmental retardation that could not be assigned to a specific syndrome (45%). Characteristics and outcomes are shown in *Online Supplementary Table S3* (developmental delay, n=8) and *Online Supplementary Table S5* [all other pre-existing conditions (n=14)], respectively.

For the 22 patients with non-classifiable pre-existing conditions, both 5-year EFS and OS rates were 57%±11% (Figure 2A and B) after a median follow up of 4.95 years (range 1.39-14.68 years). The 5-year CIR and CID were 33%±9% and 3%±3%, respectively (Figure 3A and B).

Secondary malignancies after NHL

Among the cohort of 151 patients with cancer predisposition syndromes and PIDs not further specified, 21 (14%) developed another malignancy with a 10-year cumulative incidence of SMLs of 24%±5% (*Online Supplementary Table S6* and *Online Supplementary Figure S2A*). There were no SMLs among the 62 patients with genetic diseases not known to be associated with an increased cancer risk (n=40) and non-classifiable pre-existing conditions (n=32).

Eleven of 21 (52%) patients suffered from a CMMRD, 4 (19%) from NBS, 3 (14%) from AT, and 1 patient each from WAS (5%), NF1 (5%), and XLP (5%). The 15-year cumulative incidence of SMLs according to the pre-existing condition is shown in *Online Supplementary Figure S2B*; however, curves for WAS, NF1 and XLP have to be interpreted very cautiously due to the very small number of patients and events.

Male-to-female ratio was 15:6. The distribution of histological subtypes at primary diagnosis was: mature B-cell NHL (n=8, 38%), lymphoblastic lymphoma (T-LBL, n=11, 52%, and BCP-LBL, n=1, 5%), and 1 T-cell NHL not fur-

Table 3. Clinical and laboratory characteristics and outcome of non-Hodgkin lymphoma patients in 2 categories of immunodeficiencies not further specified.

	PID n.f.sp.	CVID
N. patients	20	7
Sex		
Male	10 (50%)	4
Female	10 (50%)	3
Age (years) at dg.		
Median	4.75	9.67
Range	0.7-15.5	1.25-17.84
Histology		
Mature B-NHL	16 (76%)	5
Burkitt lymphoma	0	1
DLBCL	11	3
MZL	1	1
B-cell NHL n.f.sp.	4	0
T-LBL	1 (5%)	0
BCP-LBL	0	0
ALCL	1 (5%)	1
PTCL	2 (10%)	1
Stage of disease		
I	1 (5%)	1
II	3 (15%)	1
III	8 (40%)	2
IV	4 (20%)	2
Not available	4 (20%)	1
LDH		
≥500 U/l	6 (30%)	1
<500 U/l	8 (40%)	4
Not available	6 (30%)	2
Relapse/progression	3 (14%)	1
Second malignancy	0	0
Death	9 (45%)	5
Disease-related	1	1
Therapy-related	8	3
SML-related	0	0
Underlying PID	0	1
In CR	11 (55%)	2 (29%)
Follow up (years)		
Median	3.28	3.90
Range	0.85-14.56	0.92-6.88

PID n.f.sp.: primary immunodeficiency not further specified; CVID: common variable immunodeficiency; N.: number; dg.: diagnosis; B-NHL: B-cell non-Hodgkin lymphoma; TLBL: T-cell lymphoblastic lymphoma; BCP-LBL: B-cell precursor lymphoblastic lymphoma; ALCL: anaplastic large cell lymphoma; PTCL: peripheral T-cell lymphoma; DLBCL: diffuse large B-cell lymphoma; MZL: marginal zone lymphoma; n.f.sp.: not further specified; LDH: lactate dehydrogenase; SML: secondary malignancy; CR: complete remission.

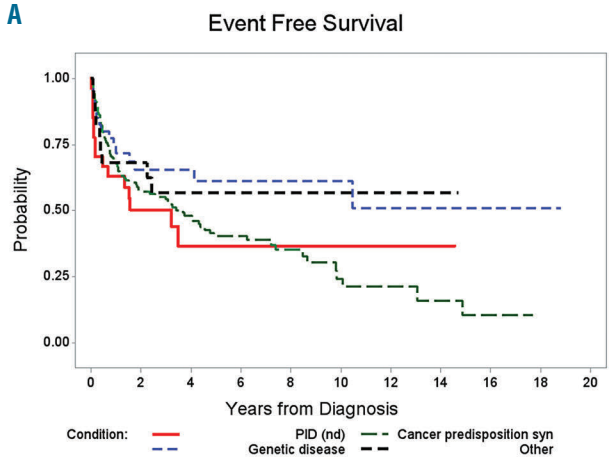
ther specified (5%). The subtypes of SML were: an NHL other than seen at primary diagnosis (n=8, 38%), brain tumor (n=5, 24%), colorectal carcinoma (n=4, 19%), myelodysplastic syndrome (n=1, 5%), hepatoblastoma (n=1, 5%), ALL (n=1, 5%), and acute myeloid leukemia (n=1, 5%).

Eighteen patients (86%) died, 14 (78%) from the SML itself, 1 (6%) from relapse of primary NHL, and 1 (6%) from therapy-related toxicity; the cause of death was not available for 2 (11%) patients. The remaining 3 patients (14%) are surviving in CR after a median follow up of 9.19 years (range 4.10-9.26 years). The 7-year OS rate for the 21 patients was 41%±11% (*Online Supplementary Figure S3*). Analysis of 5-year OS rates according to the pre-existing condition was not possible due to the very small number of patients and events.

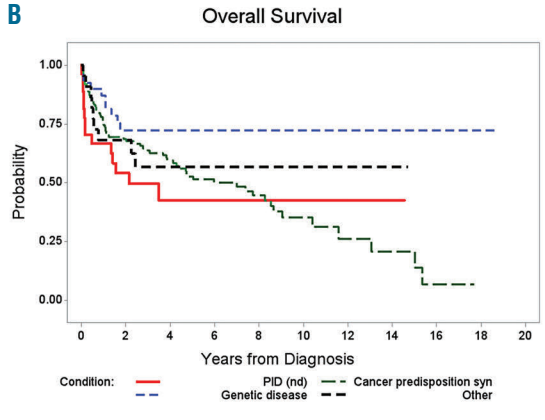
Outcome in patients with NHL and pre-existing conditions according to histological subtypes

We compared outcome of the different histological subtypes (mature B-cell NHL *vs.* T- and BCP-LBL *vs.* other NHLs) among the 5 largest distinct entities (diagnosis >20 patients) included in the survey: AT (n=32), NBS (n=26), CMMRD (n=21), PIDs not further specified (n=27), and genetic diseases not known to be associated with an increased cancer risk (n=40). However, due to the very small number of patients and events, along with the distribution of histological subtypes, we could not calculate EFS, OS, CIR or CID. Descriptive results are shown in *Online Supplementary Table S7*. We also wanted to compare outcome of the different histological subtypes (mature B-cell NHL, T- and BCP-LBL and other NHLs) across the 5 largest distinct entities (diagnosis >20 patients) included in the survey. However, again, due to the very small number of patients and events along with the distribution of histological subtypes, we could not calculate EFS, OS, CIR or CID. Descriptive results are shown in *Online Supplementary Table S8*.

Comparisons of the initial characteristics (sex, age, histological sub-entities and stage of disease) of the 3 major



Cancer predisposition syndromes	(n=124, 78 events):	5-year EFS rate: 40%±5%
Primary immunodeficiencies n. f. sp.	(n=27, 15 events):	5-year EFS rate: 37%±11%
Genetic diseases	(n=40, 15 events):	5-year EFS rate: 61%±8%
Other conditions	(n=22, 9 events):	5-year EFS rate: 57%±11% P=0.11



Cancer predisposition syndromes	(n=124, 67 events):	5-year OS rate: 53%±5%
Primary immunodeficiencies n. f. sp.	(n=27, 14 events):	5-year OS rate: 43%±11%
Genetic diseases	(n=40, 10 events):	5-year OS rate: 72%±8%
Other conditions	(n=22, 9 events):	5-year OS rate: 57%±11% P=0.0332

Figure 2. Five-year event-free (A) and overall survival (B) rates of the 124 patients with a cancer predisposition syndrome, 27 patients with a primary immunodeficiency (PID) not further specified, 40 patients with genetic diseases and 22 patients with non-classifiable pre-existing conditions.

histological subtypes (mature B-cell NHL, LBL and ALCL), including the 151 patients with cancer predisposition syndromes and PIDs not further specified only, with a representative cohort from the literature (NHL-BFM 95 trial for B-NHL and LBL, and EICNHL ALCL99 trial) are shown in *Online Supplementary Table S9*.[31,34,43]

Discussion

The current analysis represents by far the largest cohort of children and adolescents up to 19 years of age with NHL and a pre-existing condition (n=213) reported in the literature. This retrospective study was only made possible by the collaborative effort of the two largest consortia in pediatric and adolescent NHL: the EICNHL and the i-BFM SG. The results presented here not only show the wide spectrum of possible pre-existing conditions, that for further analysis had been subdivided into 4 subcategories, but also show conditions which have not yet been observed with the development of NHL, including genetic diseases such as α-1 antitrypsin deficiency and CTP synthase 1 deficiency, as well as chromosomal conditions such as Smith-Magenis syndrome, Silver-Russel syndrome, Cri-du-chat syndrome, Turner syndrome or Triple X syndrome.[44] Since it seems unlikely that particularly the third subcategory (i.e. genetic diseases without a known cancer risk) should include so many newly discovered lymphoma-prone disorders, the results might simply represent coincidental findings. Nevertheless, a prospective evaluation of the associated NHL subtypes, their therapy and its tolerance, as well as outcome, could be of vital importance to treating physicians, especially in view of the retrospectively high relapse rate observed.

Not surprisingly, the analysis of those 151 patients with cancer predisposition syndromes and PIDs not further specified demonstrated that patients with NHL and a pre-existing condition have an inferior EFS (5-year EFS:

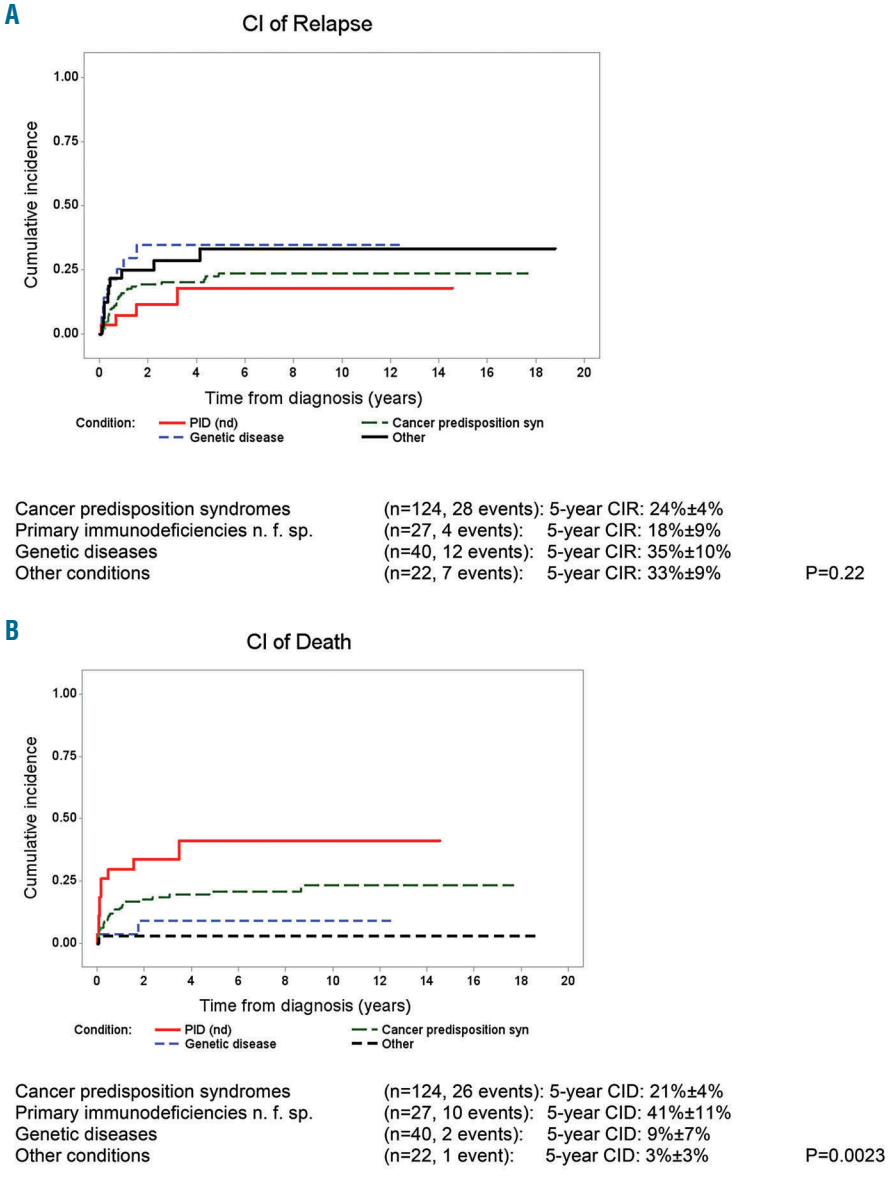


Figure 3. Five-year cumulative incidence rates of relapse (A) and treatment-related death (B) of the 124 patients with a cancer predisposition syndrome, 27 patients with a primary immunodeficiency (PID) not further specified, 40 patients with genetic diseases and 22 patients with non-classifiable pre-existing conditions.

40%±4%) with a large proportion of deaths being therapy-related (5-year CID: 24%±4%), as compared to what is known from patients with NHL without a pre-existing condition.[27,28,31,34,35,37,38] A comparative analysis showed long-term results from the NHL-BFM SG with 3-year EFS rates of 89%±1% for mature B-cell NHL in trial NHL-BFM 95 [n=505 (toxic death n=10)] and 5-year EFS rates of 82%±3% and 88%±3% for stage III/IV T-LBL in trials NHL-BFM 95 [n=156 (toxic death n=2)] and 90+86 [n=163 (toxic death n=3)].[31,34] Moreover, 2-year EFS rates were 74.1% (95%CI: 69.2%-78.4%) for ALCL in the EICNHL trial ALCL99 [n=352 (toxic death n=4)] and 45%±5% for an international cohort of 143 patients with PTCL.[43,45] Notably, 36 of 143 (25%) had a pre-existing condition and fared very poorly, with 5-year EFS rates of 11%±7%.[45]

In summary, half of our patients suffered from an event, with half of these patients experiencing a relapse/progression; the other half died from therapy-related toxicity. Moreover, our study also discovered a male predominance in children and adolescents with pre-existing conditions and NHL (approx. 65% were male) for which there is still no explanation, and further studies are warranted to reveal the biological background of why the male sex is more often affected.[17]

The largest subgroup of patients comprised well-known cancer predispositions (n=124) with DNA repair defects such as AT (n=32), NBS (n=26), and CMMRD (n=21), accounting for 65% of all patients in this subcategory. Within these 3 predominant groups, we identified variations in the NHL histological subtypes. Whilst mature B-cell NHL was seen in approximately 85% of patients with AT (with DLBCL 2.8-times more frequent than Burkitt lymphoma), patients with NBS had a high incidence of PTCL (approx. 25%) and patients with CMMRD had a very high incidence of T-LBL (approx. 80%).

The association of DNA repair defects with lymphoid malignancies is well known and has been repeatedly reported with acceptable outcomes which can, however, be improved.[5-8,10,16,22,46]

Our analysis showed that while approximately 50% of AT patients died from therapy-related toxicity, death from NHL and therapy-related complications was evenly distributed among NBS patients. In comparison, the NHL-BFM SG reported on 37 patients with chromosomal instability syndromes (AT and NBS) with 5-year EFS rates of 48%±12% for 16 patients with ALL/T-LBL (relapse/progression n=2; SML n=2; treatment-related death n=2; alive n=10) and 51%±16% for 21 patients with mature B-cell NHL (relapse/progression n=2; SML n=2; treatment-related death n=1; dead from underlying disorder n=4; alive n=12).[6] Of our CMMRD patients, nearly 75% died, either from NHL or another SML. This extremely high mortality rate also confirms that CMMRD has to be diagnosed in a timely fashion to allow tumor surveillance, and that adapted chemotherapies are necessary to treat the different highly resistant childhood cancers occurring in this group of patients.[9,47]

In contrast, patients with XLP (n=11) and WAS (n=7), mainly suffering from mature B-cell NHL (5 of 11 and 2 of 5 with DLBCL), had a comparatively good outcome with 70%-90% of the patients in first CR. Among the other diagnoses of cancer predisposition syndromes, death from therapy-related complications accounted for most events. Thus, although not all diagnoses can be viewed uniformly, our analysis showed an inferior survival (5-year OS: 53%±5%) with a large proportion of deaths being therapy-related (5-year CID: 21%±4%) for children and adolescents with NHL and a cancer predisposition syndrome, as compared to what is known from NHL patients without cancer predispositions.[27,28,31,34,35,37,38] Interestingly, despite the low number of 21 patients (13%) with a cancer predisposition who underwent allo-SCT in first CR, their outcome was rather good, with 17 (81%) of them surviving event free, suggesting that cure from both the underlying disease and NHL is possible.

The second subcategory included patients with a PID not further specified (n=27), including 7 children who were reported with a CVID. Three-quarters had mature B-cell NHLs (14 of them with DLBCL). Assuming that this group of patients could have been genetically characterized, thus belonging to defined cancer predisposition syndromes, death from therapy-related toxicity in 41%±11% of the patients highlights the same dilemma of increased therapy-related toxicity, as seen in patients with defined cancer predispositions. However, again, allo-SCT in first CR in 10 patients with 8 surviving event free suggests that long-term survival is possible.

The third subcategory was made up of patients with genetic disorders not known to be associated with an increased cancer risk (n=40) with only G6PD deficiency (n=4) seen in more than 2 patients. Notably, hemophilia A, cystic fibrosis, α-1 antitrypsin deficiency, Prader-Labhart-Willi syndrome and Williams-Beuren syndrome were reported each in 2 patients, and approximately 65% of all patients had a mature B-cell NHL. Outcome analysis showed that, in this cohort of patients, therapy-related death (5-year CID: 9%±7%) was not in the same range as for the first 2 subcategories, but that the 5-year CIR of 35%±10% was rather high as compared to what is seen in the pediatric NHL population without genetic diseases.[27,28,31,34,35,37,38] In comparison, long-term results from the NHL-BFM SG showed only 39 (8%) tumor failures for mature B-cell NHL in trial NHL-BFM 95 (n=505), and 18 (12%) and 14 (9%) tumor failures for stage III/IV T-LBL in trials NHL-BFM 95 (n=156) and 90+86 (n=163).[31,34] In addition, 84 patients (24%) with ALCL had a tumor failure in the EICNHL trial ALCL99 (n=352).[43]

However, whether the observed increase in relapse rates in NHL patients with genetic disorders without a known cancer risk was due to the inability to administer sufficient anti-neoplastic therapy could not be assessed as details on therapy reduction and modification were lacking.

Although we had a unique opportunity to analyze a cohort of more than 200 patients with NHL and an underlying condition, the present study has several limitations. 1) Undoubtedly, a certain number of patients with pre-existing conditions that were not documented in the participating countries upon diagnosis of NHL is missed given the inherent features of this type of project. In addition, the retrospective nature may have led to both an under- and an over-representation of certain diagnoses, thereby influencing results; this drawback was managed by subcategorizing the study cohort and limiting most outcome analyses to the 3 largest subcategories only. 2) Since we did not ask for all patients with NHL with or without a pre-existing condition within the respective countries and centers to be included in the study, we were not able to assess the relative frequency of constitutional

disorders within the general NHL population. Therefore, we were not able to compare characteristics and outcome between them. 3) The retrospective nature of the study, and lack of detailed data on chemotherapy and dose modifications, therapy-related toxicities and conditioning regimens used for SCT, did not allow us to assess the impact of these parameters on outcome. 4) As we had not asked for all patients with pre-existing conditions registered within the respective countries to be included in the study, we could also not provide the relative risk of patients with a respective pre-existing condition to develop NHL, as compared to the general population. 5) Unfortunately, we also had no information on whether the diagnosis of, in particular, some DNA repair defects and other PIDs was made before the diagnosis of NHL or whether unexpectedly severe toxicity during therapy led the treating physicians to search for underlying diseases and to subsequent diagnosis.

However, our large collaborative effort could be the first step towards establishing a multinational registry for children and adolescents with pre-existing conditions and NHL, thus not only identifying which disorders are particularly prone to develop NHL, but also facilitating therapy trials that consider the specific needs of these patients. At least those subcategories of cancer predisposition syndromes and PIDs not further specified represent distinct subsets of patients who are especially prone to treatment-related toxicity and may need special vigilance when receiving standard or modified/reduced-intensity chemotherapy or allo-SCT.

Acknowledgments

We thank all participating institutions and physicians for their support of the study. This EICNHL and i-BFM paper was written on behalf of the Berlin-Frankfurt-Münster (BFM) Study Group (Austria, Germany, Switzerland, Czech Republic), Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), Société Française de Lutte contre les Cancers et Leucémies de l'Enfant (SFCE), United Kingdom Children's Cancer and Leukemia Study Group (CCLG), Belgian Society of Pediatric Hematology and Oncology, Dutch Childhood Oncology Group (DCOG), Hungarian Pediatric Oncology Network, Israel's Society of Pediatric Hematology and Oncology, Slovenian Society of Hematology and Oncology, Slovakian Pediatric Association (Section of Pediatric Hemato-Oncology), Serbian Society of Hematology and Oncology, Polish Society of Pediatric Oncology and Hematology, Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), Hong Kong Pediatric Hematology and Oncology Study Group (HKPHOSG) and three single institutions from Canada (Toronto), Belarus (Minsk) and Russia (Moscow).

Funding

This work was supported by Cancer Research United Kingdom, the Forschungshilfe Station Peiper (BFM Germany), the St. Anna Kinderkrebsforschung (BFM Austria), the Czech Ministry of Health supported projects for conceptual development of research organization 00064203 and 65269705 (BFM Czech Republic), Project N. LQ1605 of the National Program of Sustainability II (Czech Republic) and the Ministry of Health, Labour and Welfare of Japan (JPLSG).

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