haematologica
Journal of The Ferrata Storti Foundation

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Haematologica 2020 [Epub ahead of print]

Citation: Olga Moser, Martin Zimmermann, Ulrike Meyer, Wolfram Klapper, Ilske Oschlies, Martin Schrappe, Andishe Attarbaschi, Georg Mann, Felix Niggli, Claudia Spix, Udo Kontny, Thomas Klingebiel, Alfred Reiter, Birgit Burkhardt, and Wilhelm Woessmann. Second malignancies after treatment of childhood non-Hodgkin lymphoma – a report of the Berlin-Frankfurt-Muenster study group. Haematologica. 2020; 105:xxx
doi:10.3324/haematol.2019.244780

Title page

Second malignancies after treatment of childhood non-Hodgkin lymphoma – a report of the Berlin-Frankfurt-Muenster study group.

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The study represents original work and has not been published before.

Disclosures:

Martin Schrappe:
Honoraria: prIME Oncology; Speakers' Bureau: Baxalta; Research Funding: Sigma Tau, Baxter, Medac
Thomas Klingebiel:
Consulting or advisory role: Novartis (07/2016)
Andishe Attarbaschi:
Honoraria: Jazz Pharmaceuticals; Consulting or advisory role: Jazz Pharmaceuticals

Nothing to disclose: Olga Moser, Martin Zimmermann, Ulrike Meyer, Wolfram Klapper, Ilske Oschlies, Georg Mann, Felix Niggli, Claudia Spix, Udo Kontny, Alfred Reiter, Birgit Burkhardt, Wilhelm Woessmann

Word count

Abstract: 249, main text: 3883, tables: 4, figures: 3, supplemental file: 1

Acknowledgments

We acknowledge the contribution of past and present coordinators and medical records technicians of the BFM study group for helping to establish this dataset. We thank all the clinicians who entered patients into the subsequent NHL-BFM trials and the children and families who agreed to take part. This study was supported by the Forschungshilfe Station Peiper (Research Support Peiper), Germany, and the Deutsche Kinderkrebsstiftung (German Childhood Cancer Foundation) for the NHL-BFM Registry 2012 (DKS 2014.11 A/B), and the St. Anna Kinderkrebsforschung (Children's Cancer Research Institute), Austria.

Abstract

Second malignant neoplasms pose a concern for survivors of childhood cancer.

We evaluated incidence, type and risk factors for second malignant neoplasms in patients included in Berlin-Frankfurt-Muenster protocols for childhood non-Hodgkin lymphoma.

3590 patients <15 years of age at diagnosis registered between 01/1981 and 06/2010 were analyzed. Second malignant neoplasms were reported by the treating institutions and the German Childhood Cancer Registry.

After median follow-up of 9.4 years (Quartile, Q1 6.7 and Q3 12.1) 95 second malignant neoplasms were registered (26 carcinomas including 9 basal cell carcinomas, 21 acute myeloid leukemias/myelodysplastic syndromes, 20 lymphoid malignancies, 12 CNS-tumors, and 16 other). Cumulative incidence at 20 years was 5.7±0.7%, standard incidence ratio excluding basal cell carcinomas was 19.8 (95% CI 14.5-26.5). Median time from initial diagnosis to second malignancy was 8.7 years (range: 0.2-30.3). Acute-lymphoblastic-leukemia-type therapy, cumulative anthracycline dose, and cranial radiotherapy for brain tumor-development were significant risk factors in univariate analysis only. In multivariate analysis including risk factors significant in univariate analysis, female sex (HR 1.87, 95% CI 1.23-2.86, p=0.004), CNS-involvement (HR 2.24, 95% CI 1.03-4.88, p=0.042), lymphoblastic lymphoma (HR 2.60, 95% CI 1.69-3.97, p<0.001), and cancer-predisposing condition (HR 11.2, 95% CI 5.52-22.75, p<0.001) retained an independent risk.

Carcinomas were the most frequent second malignant neoplasms after non-Hodgkin lymphoma in childhood followed by acute myeloid leukemia and lymphoid malignancies. Female sex, lymphoblastic lymphoma, CNS-involvement, or/and known cancer-predisposing condition were risk factors for second malignant neoplasm-development. Our findings set the basis for individualized long-term follow-up and risk assessment of new therapies.

Introduction

Second malignant neoplasms (SMN) represent a serious long-term risk after treatment of children with cancer. Reported cumulative incidences of SMN after childhood cancer vary between 3 and 11% at 20-30 years depending on the first cancer, type of treatment and cumulative drug doses.[1-5] No lifetime cumulative incidence has been established so far. A recently published study of the German Childhood Cancer Registry (GCCR) has shown a cumulative incidence of 8.3% within 35 years after first cancer in childhood.[6] Analysis of SMN after treatment for childhood non-Hodgkin lymphoma (NHL) showed cumulative incidences between 3 and 10% at 20-30 years after NHL diagnosis; the reported standard incidence ratios (SIR) for SMN varied between 2.4 and 12.0.[1-5, 6-10] Most information is derived from cancer registries in population-based studies on SMN after childhood cancer.[1-9] These studies lack a detailed information about the NHL-subtypes and specific treatments. Two previous studies focused on SMN after childhood NHL.[9,10] One of them limited the analysis to 5-year survivors of NHL, thus omitting most of the hematologic SMN that occur within 5 years of first diagnosis.[9] Two further studies about late health outcomes after treatment of childhood NHL included incidences of SMN , however, restricted the analysis to 5- and 10-year survivors of NHL, respectively.[11,12]

Studies on SMN after NHL in adulthood report an increased incidence of leukemia and solid tumors.[13,14] A meta-analysis concerning the risk of SMNs in adult NHL survivors detected a 1.88-fold increased risk for SMN in comparison with the general population.[14]

Treatment strategies for children with NHL differ from those used in adults with respect to the cumulative drug doses and the application of radiation. Whereas radiotherapy was largely omitted during the 1970s in the pediatric Berlin-Frankfurt-Muenster (BFM)-trials, it is applied in the treatment of most adults with NHL and bulky disease (supplementary tables S1, S2).

In addition, the incidence of SMN may vary according to NHL subtype and treatment regimen, and may also be influenced by genetic and specific host factors.

We analyzed the incidence and type of SMN as well as risk factors for the development of SMN in a population-based large cohort of children treated for NHL with uniform subtype-specific therapy regimens according to the NHL-BFM trials. Cumulative drug doses and the backbone of the NHL-BFM trials remained stable over the analysis period of 30 years.

Methods

From 01/1981 to 06/2010, 4184 children from 99 BFM-institutions diagnosed with NHL were registered into the studies ALL/NHL-BFM-81, -83, -86, NHL-BFM-90, -95, ALCL-99, EURO-LB-02, LBL-Register and B-NHL-BFM-04 after informed consent of the patient and/or guardians. The studies were conducted according to the Declaration of Helsinki. Approval was obtained from ethical committees of the investigators. 3590 patients <15 years of age at diagnosis, were included in the analysis by 04/2017 (Figure 1).

NHL were classified using classifications at the time of diagnosis [15,16,17] (supplement). Central reference pathology- and/or immunology-review was performed in over 90% of cases. Patients were stratified according to the St Jude staging system[18] and treated on one of the NHL-BFM-protocols listed above. Patients with lymphoblastic lymphoma (LBL) received an acute-lymphoblastic-leukemia (ALL)-type BFM-regimen consisting of eight-drug induction, consolidation, re-intensification, and maintenance up to two years of therapy. Patients with mature B-cell-NHL or anaplastic large-cell-lymphoma (ALCL) received 2-6 courses of five-day block-type chemotherapy as previously reported. [19-23]All cumulative drug- and radiation doses are listed in the online supplemental tables S1 and S2.

Long-term follow-up of patients was assured by the NHL-BFM datacenter and the GCCR (General Information on data collection by the GCCR: www.kinderkrebsregister.de/english/). Details on follow-up are described in the online supplemental appendix.

For the purpose of this evaluation, histopathology information about first and second malignancy was re-reviewed in all patients. If required, complementary affirmative investigations were performed by the central reference pathology. Non-lymphoid and lymphoid malignancies fulfilling the criteria depicted below were considered as proven SMN. In cases of multiple SMN after NHL, only the first second cancer was counted.

Statistical analysis

The risk of SMN was estimated by cumulative incidence functions for SMN and death as competing events. Functions were compared using Gray test. 95 % confidence intervals (CI) were calculated using standard methods.[24]

Survival after SMN was calculated from the date of SMN-diagnosis to the date of death or last follow-up, respectively. Probability of survival was calculated according to Kaplan-Meier.[25]

SIRs were calculated as the ratio of observed SMNs and expected number of malignancies, as described by Scholz-Kreisel et al.[6] . Age-, sex-, and calendar year–specific rates from the GCCR were used to calculate expected numbers for cases below 15 years. These data are complete and cover all diagnoses reported here. Population-based incidence rates for cases older than 15 years were not available for the entire period and all diagnoses. Therefore, the SIR was calculated for a subgroup of the cohort without basal cell carcinoma.

The contribution of factors to the development of SMN was estimated with the Cox proportional-hazards model. The clinical and biologic features analyzed included age at first diagnosis, sex, NHL-entity, -stage, therapy-type and known cancer-predisposing condition (CPC). The doses (as per protocol) of epipodophyllotoxins, cyclophosphamide/ifosfamide (dose equivalence ratio 1:4), anthracyclines (dose equivalence ratio 1:1), cytarabine, asparaginase were analyzed, further stem-cell transplantation, and cranial radiotherapy. Statistical analysis was performed using SAS program (SAS, version 9.4; SAS Institute Inc, Cary, NC).

Results

Patient characteristics

Patient characteristics are shown in table 1. Because of age restriction applied by the GCCR until 2008, we included only patients <15 years at first diagnosis of NHL in our analysis to ensure the most accurate assessment of the incidence of SMN in the study population. The analyzed group included 57 patients with known CPC, namely primary and secondary immune deficiencies, Gorlin-, mismatch-repair-deficiency syndromes, neurofibromatoses, Fanconi anaemia. There was no systematic screening for CPC in the study population. Reported patients were identified by the presence of clinical immune deficiency, and/or signs of the syndromes stated above. Investigations for CPC were prompted by multiple-cancer development and/or diminished therapy tolerance in some cases. Six of 57 patients with CPC received radiotherapy. Altogether, 24.7% of all 3590 patients received ALL-type therapy and 75.3% B-NHL-type regime. 450 patients in the analyzed cohort (12.5%) suffered from relapse of the NHL. Treatment for relapsed disease consisted of individualized chemotherapy. 252 patients received consolidation by stem cell transplantation. Patients developing any kind of SMN did not significantly differ from those who did not with respect to the age at diagnosis, stage of NHL, or bone-marrow involvement.

With a median follow-up of 9.4 years (Quartile, Q1 6.7 and Q3 12.1), the probability of survival at 20 years was 83%, SE=0.01 for the total group of 3590 patients.

Second malignant neoplasms (SMN)

95 SMN were documented: 26 carcinomas (including 9 basal-cell carcinomas), 21 acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), 20 second lymphoid malignancies (12 NHL, 4 ALL, 4 Hodgkin disease), 12 malignant CNS-tumors, 5 sarcomas, 5 malignant melanomas, and 7 other SMN (figure 1, table 3).

Second lymphoid malignancy was considered to be proven when (i) in lymphoid malignancy there was a lineage change, i.e., B lineage to T lineage and vice versa, (ii) in lymphoid malignancy there was a change with respect to the differentiation compartment, i.e., from a precursor B (or T) neoplasm to mature B (or T) neoplasm or vice versa, (iii) in Burkitt lymphoma/Burkitt leukemia there was a MYC rearrangement at different break points between the first and the second cancer or (iiii) in mature B-NHL there was a different immunoglobulin light-chain restriction between the first and second malignancy i.e. λ to κ or vice versa. Not included as SMN were eight late-recurring lymphoid malignancies with different clonal rearrangements of IgH- and T-cell-receptor-genes, but no differences with respect to discriminators listed above (i-iiii), since clonal evolution in these cases cannot be excluded. Evaluation of clonal origin via multiplex-PCR (BIOMED-2 method[26]) was performed for all available tumor samples in cases of second lymphoid malignancy.

We also observed 20 benign neoplasms (eight low-grade meningeomas, five adenomas, four osteochondromas, one pilomatrixoma, chondroblastoma, neurinoma each).

The SIR for all SMN without basal cell carcinoma was 19.8 (95% confidence interval (CI) 14.5-26.5).

Cumulative incidence of all SMN at 20 years was 5.3% (SE=0.7) (figure 2A). Cumulative incidences of distinct SMN-groups are depicted in figure 3. The median age at diagnosis of NHL within the population of <15 years was 8.1 years (range: 0.3-14.9) for patients who subsequently developed a SMN. The median time from first diagnosis of NHL to SMN was 8.7 years (range: 0.2-30.3). The median time to development of all carcinomas was 15.9 years (range: 0.7-30.3), and 11.6 years (range: 0.7-23.7) excluding basal-cell carcinomas. The median time was 3.1 years (range: 0.3-8.7) for AML/MDS, 5.7 years (range: 1.5-20.2) for second lymphoid malignancy, and 8.6 years (range: 0.8-17.3) for CNS-tumors, respectively (table 3). Carcinomas of the gastrointestinal tract and basal-cell carcinoma were the most

frequent carcinomas (9 each) (table 3). Six of the nine gastrointestinal tract-carcinomas occurred after a T-cell LBL.

Univariate analysis of risk factors (table 1)

Cumulative incidence of SMN was significantly higher among patients with LBL (9.3% at 20 years, SE=1.9%), as compared to patients with other NHL-entities (3.9% at 20 years, SE =0.8%, p<0.0001) (figure 2B). In patients with LBL, both carcinomas and AML/MDS were the most common SMN (14 each), accounting for 72% of all SMN after LBL. The cumulative incidence of AML/MDS was 1.8%, SE=0.5% after LBL as compared to 0.1%, SE=0.1% after mature B-NHL (p<0.0001). Carcinomas had a higher cumulative incidence in LBL compared to mature B-NHL as well (4.6% SE=1.5% vs 2.5% SE=0.7%, p=0.04). Second lymphoid malignancy represented the largest SMN-group (34%) after mature B-NHL. Female sex was a risk factor for SMN (20-year cumulative incidence 8.4% vs. 4.0% in males, p=0.0008) (table 1). Patients with known CPC were at significantly higher risk for development of SMN (cumulative incidence 19.9% vs. 4.9%, p<0.0001) (figure 2C). The majority of patients with CPC were female (66.7%). The most frequent SMN in patients with CPC was another lymphoid malignancy (table 3, Suppl. table S3). With a median age of 6.4 years (range 1.3-9.6) at primary NHL diagnosis, patients with CPC were younger than other patients with SMN. Neither disease stage nor bone marrow involvement at primary diagnosis were significant risk factors (table 1).

Only patients with LBL received ALL-type therapy. Only ALL-type therapy contains >200mg/m^2 doxorubicin equivalent. Accordingly, the cumulative incidence of SMN at 20 years was significantly higher after ALL-type therapy (8.7%, SE=1.7) as compared to B-NHL-type therapy (3.7%, SE=0.7; p=0.0002) and among patients who had received >200mg/m^2 doxorubicin equivalent (8.7, SE=1.8) as compared to patients receiving less (4.3, SE=0.8, p<0.0001). Exposure to etoposide was not a risk factor for AML/MDS (results not

shown). 76% of patients who developed AML/MDS did not receive any epipodophyllotoxins. The use of high cumulative doses of alkylating agents was not associated with higher incidence of SMN (table 1).

Patients who received cranial radiotherapy were at significantly higher risk for developing a second CNS malignancy (p=0.01), (table 1).

Stem cell transplantation correlated with SMN-development among patients who received B-NHL-type therapy (cumulative incidence 10.4%, SE=3.9, vs. 2.8, SE=0.6; p=0.005).

Because the previous reports of SMN after childhood cancer did not include non-melanoma skin cancer, for comparison purpose we performed cumulative incidence analyses excluding basal-cell carcinoma. Cumulative incidence of all SMN excluding basal-cell carcinoma at 20 years was 4.8% (SE=0.7). Cumulative incidence of SMN remained significantly higher among patients with LBL (8.6% at 20 years, SE=1.7%), as compared to patients with other NHL-entities (3.4% at 20 years, SE=0.7%, p<0.0001), and in patients with known CPC (19.6% at 20 years, SE=7.1), as compared to patients without known CPC (4.4% at 20 years, SE=0.7, p<0.0001) after exclusion of basal-cell carcinoma from the analysis.

Multivariate analysis of risk factors

In a stepwise Cox regression analysis taking into account risk factors significant in univariate analysis, which are listed in table 1, only female sex (hazard ratio (HR) 1.9, CI 1.2-2.9, p=0.004), CNS-involvement (HR 2.2, CI 1.0-4.9, p=0.04), diagnosis of LBL (HR 2.6, CI 1.7-4.0, p<0.001), and a known CPC (HR 11.2, CI 5.5-22.8, p<0.001) represented independent risk factors for the development of SMN (table 2). Looking for the risk factors for the development of AML/MDS, a diagnosis of LBL (HR 12.0, CI 3.8-37.0, p<0.001), CNS-involvement (HR 5.2, CI 1.5-18.5, p=0.01) and a known CPC (HR 8.8 (CI 1.2-67.3), p=0.04) showed a significant association.

Outcome after SMN

Survival at 10 years after diagnosis of the SMN was 47%, SE=6.4, the worst prognosis carrying AML/MDS with a 10-year survival of 26.5%, SE=11.6, followed by CNS-malignancy (43.6%, SE=15.5). Patients with solid secondary tumors outside the CNS had a 10-year survival of 50.8%, SE=13.0 and patients with second lymphoid malignancy 57.8%, SE=13.3, respectively. Patients with known CPC had a survival of only 11.1%, SE=10.5. Nine patients (six with known CPC) with SMN developed a third malignant neoplasm (tables 3, 4).

Discussion

We present the incidence and types of SMN as well as risk factors for the development of SMN in the to date largest cohort of patients who were treated for NHL as children according to subtype-specific BFM-type therapy regimens with stable cumulative drug doses over the analysis period. The estimated 20-year cumulative incidence of SMN of 5.3±0.7%, (4.8±0.7% without basal-cell carcinomas), among 3590 patients is comparable to the one reported by Leung et al.[10] in a cohort of 497 children with NHL (4.8±1.3% at 20 years). An analysis of 456 French and British 3-year survivors of pediatric NHL showed 25-year cumulative incidence of solid SMN of 10%, and a relative risk of 12%.[1] The CCSS group reported 20-year cumulative incidence of SMN of 3% (SIR of 3.9) in 1082 5-year survivors of pediatric NHL.[9] Since this study focused on solid-tumor SMN most of the AML/MDS that occur within 5 years of first NHL-diagnosis and all secondary lymphomas were not included which explains the somewhat lower cumulative incidence compared to our study. In an updated CCSS-report from 2010, a 30-year cumulative incidence of 5.8% and SIR of 4.1% was reported for the same cohort of patients.[8] The observation of increasing cumulative incidence with longer observation time is reflected in our study by the missing plateau for secondary carcinomas after NHL-therapy.

Analyses in the US Surveillance, Epidemiology, and End Results (SEER) program showed 5.3-fold elevated risk for SMNs after NHL compared to the normal population in patients diagnosed before the age of 18 years with significantly higher risks for breast cancer and acute non-lymphoid leukemia in a cohort of 1150 patients treated between 1973 and 2002.[2] Another SEER analysis in a cohort of 1832 5-year survivors of childhood NHL under 15 years of age at initial diagnosis reported SIR of 3.3 for SMN.[4] Focusing on 4310 NHL survivors treated with chemotherapy only, the CCSS-group reported a lower SIR of 2.4 for SMN occurring ≥5 years from initial diagnosis without non-melanoma skin cancers.[5] The evaluation of late outcomes in a cohort of 200 childhood NHL patients having survived for

≥10-years in the St Jude Lifetime Cohort Study revealed SIR of 6.3 for SMN, with none occurring in not-irradiated individuals.[12] We observed a higher SIR of 19.8 (without basal-cell carcinoma), which is similar to the SIR after acute lymphoblastic leukemia reported by the GCCR.[6] Different inclusion criteria of patients regarding the age at initial diagnosis, varying restriction of the latency period to SMN-development, exclusion or inclusion of some SMN types (e.g., lymphoma), and possibly differences in the treatment regimen may influence variations in the SIR estimates. Younger age at initial diagnosis (<15 years), no restriction of latency period to SMN-development, inclusion of patients with known CPC, and inclusion of second lymphoid malignancies explain a higher SIR in our cohort of patients treated by contemporary NHL-protocols with prophylactic brain irradiation only in LBL-patients. We cannot exclude that variations of the estimate cancer incidence in the control population might interfere regarding the different SIR-estimates as well.

Identified risk factors for SMN development in the published studies were female sex,[9] previous radiotherapy,[1,2,8,9,12] and use of epipodophyllotoxins (for development of sAML/MDS).[2,10] Cumulative incidence of SMN in our study was significantly higher in patients with LBL receiving ALL-type therapy as compared to patients with other NHL-entities receiving B-NHL-type therapy, mainly attributable to the high incidence of sAML/MDS and carcinomas in LBL-patients. In contrast to Leung[10] and Inskip[2] we could not explain the occurrence of AML/MDS after LBL by excess use of epipodophyllotoxins, as these were not part of the BFM-ALL-type treatment regimen. The anthracycline doses of 240 mg/m² doxorubicin-equivalent received by most LBL-patients could be discussed to be associated with the induction of AML/MDS. However, only four of 21 observed AML showed MLL-rearrangements characteristic for topoisomerase-II inhibitors-induced AML.[27,28] The majority of AML/MDS developed in patients with advanced stage T-LBL. An increased risk of AML was reported in pediatric patients after ALL with T-cell phenotype, too.[29] There were also single reports on lineage switch in T-ALL relapsing as AML,[30] suggesting a

common origin of precursor T- and myeloid cells. Our analysis among NHL-patients supports the above observations towards a possible common underlying mechanism predisposing some patients with T-cell precursor neoplasm to development of AML/MDS.

In an analysis of late outcomes after treatment in 570 children with B-NHL[11] who survived ≥5 years from initial diagnosis, none of the 126 children treated with the contemporary "Lymphome Malin de Burkitt (LMB) therapy" between 1987 and 1999 without radiotherapy developed a SMN. Patients treated with non-LMB protocols, including radiotherapy, had a SMN incidence rate of 2.2 per 1,000 person-years (5,871 total person-years).[11] The inclusion of second lymphoid malignancies in our cohort which accounted for 37.8% of all SMN after B-NHL and the restriction of the reported SMN to ≥5-year survivors in the earlier study[11] can explain the higher risk estimate for patients after B-NHL type therapy in our analysis of 3.9%.

The most frequent SMNs after NHL in our as well as other analyses were solid tumors, the largest group consisting of carcinomas. Compared to the hematologic SMN, the cumulative incidence estimates for solid tumors do not show a plateau after 20 years which is in line with the observation of higher estimates in the CCSS studies with longer follow-up.

Several studies demonstrated a relationship between radiotherapy and solid SMN as exemplified by the occurrence of CNS-tumors after radiotherapy for a primary CNS-malignancy or after cranial radiotherapy for ALL.[31,32] The latter was also observed in our study. In contrast to the findings of others,[1,2,8,9,12] radiotherapy was not associated with development of SMN outside the CNS in our study. This can be explained by the omission of local radiotherapy early in the BFM-studies, and consecutively, very low numbers of patients exposed to radiotherapy outside the CNS in our cohort (38 of the 3590 patients), precluding the detection of a significant impact on SMN-development in the radiation field outside the CNS.

Several patterns noticed in our cohort suggest the possible existence of unknown familial cancer syndromes predisposing to NHL and solid neoplasia.[33] Unlike previous reports[1-10] we encountered an unusual high number of gastrointestinal tract-carcinomas, most of them occurring after T-LBL. Interestingly, SIR of 67.3 for development of SMN of digestive tract after childhood NHL was also reported by Erhardt et al.[12] In three patients with gastrointestinal tract-carcinomas in our cohort a constitutional mismatch repair deficiency (CMMRD)[34] was diagnosed so far (table 4). Nine patients developed >2 malignancies, in 6 of them a CPC was diagnosed, suggesting the presence of more, as yet undiscovered CPCs. A EICNHL and i-BFM-survey revealed a 10-year cumulative incidence of SMN of 24% ± 5% among 151 children with CPC and NHL.[35] An increased cancer risk (SIR 1.5) of siblings of patients with SMN after childhood cancer also support the theory of familial susceptibility for cancer development.[3] Because of the retrospective character of our study, obtaining a detailed family history of cancer burden or further genetic investigations cannot be easily performed. Further studies are needed to address this issue.

Skin cancer as SMNs after childhood cancer has been mostly associated with radiotherapy.[36] Among the nine basal-cell carcinomas and four melanomas in our cohort, however, only six had received radiotherapy. Astonishingly, four basal-cell carcinomas developed after ALCL (without radiotherapy), an association which has not been observed so far.

Unexpectedly, the third most frequent SMN after a childhood NHL in our analysis was another lymphoid malignancy (Supplementary table S3). A high incidence of second lymphoid malignancy after NHL has not been reported so far.

Most of the second lymphoid malignancies (70%) occurred after mature B-NHL. Primary and secondary immune deficiencies, as well as defects of mismatch DNA-repair mechanisms bear susceptibility for development of NHL.[37] In our study six patients with second lymphoid malignancy had a known CPC. For the remaining 14 patients either as yet unknown

susceptibilities for development of lymphoma, or defects of immune surveillance might be discussed.

Following a large cohort of children with NHL enrolled in consecutive clinical studies with uniform treatment backbones is a strength of our study. The combined follow-up of patients by the NHL-BFM study group as well as the GCCR ensured a high probability to collect most of the SMN after NHL in childhood. Furthermore, all reports were medically validated. Careful analysis of second lymphoid tumors after NHL including comparison of tumor material from first and second tumor enabled us to distinguish second lymphoid malignancies from relapses. However, we cannot exclude an under-reporting of second lymphoid malignancies in cases of assumed relapses with similar histology and insufficient tumor material for molecular comparison. With a median follow-up time of 9.4 years (maximal 36 years) we likely captured most of the hematologic SMN, but not solid tumors. Despite the significant higher risk of SMN for patients with known CPC, we likely underestimated the frequency of CPC among children suffering from NHL, since CPC were not screened for systematically.

Genetic predisposition and immune suppression are important risk factors for development of SMN in line with previously administered chemotherapy and/or radiotherapy. Therefore efforts should be made to identify individuals with CPC. The inclusion of basic immunological examinations and using standardized questionnaires[38] about personal and family history of the patients should be discussed for all children with NHL in order to provide a better basis for long-term patient care. Our study underscores the importance of maintaining a high attention on patient follow-up beyond the pediatric age. Patients and caregivers of survivors of childhood NHL should be aware of the specific risk factors for development of SMN, with high alertness to early signs and symptoms of possible malignancy, such as carcinoma of the gastrointestinal tract or CNS tumor, in order to allow

for timely diagnosis. Also directed screening for SMN might be appropriate with the goal to improve the prognosis for the treatment of the second malignancy. In cases of late recurring lymphoid malignancies, the possibility of a SMN as opposed to relapse of the primary lymphoma should be considered with potential implications for the application of diagnostic tools (e.g. molecular genetics and clonality analysis) and treatment decisions.

In conclusion, our analysis revealed an increased risk for SMN after successful treatment of childhood NHL. The cumulative incidence of SMN was significantly higher in LBL-patients compared to the other subtypes of NHL. The diagnosis of LBL was an independent risk factor for development of AML/MDS. Patients with known CPC had significantly higher risk for development of SMNs than patients without known CPC. Solid malignancies were the most frequent SMNs followed by AML/MDS and second lymphoid malignancy.

Contributors

AR, BB, WW, and OM designed the study. AR, BB, FN, GM, and WW were trial coordinators. IO, and WK did laboratory tests. AA, AR, BB, FN, GM, MS, OM, TK, UK, and WW recruited patients for the BFM-trials. UM, MZ and CS established the dataset. MZ performed statistical analysis. AR, BB, MZ, WW, and OM analyzed data. BB, WW, and OM wrote the paper. OM had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed the draft of the paper submitted for publication.

Declaration of interests

We declare no competing interests.

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Tables

Table 1. Analysis of risk factors for the development of second malignant neoplasms (SMN) after Non-Hodgkin lymphoma (NHL) in children < 15 years of age at diagnosis, treated in one of the consecutive NHL-BFM studies NHL-BFM-81, through EURO-LB-02/B-NHL-04

Table 1: Risk factors for development of SMN, univariate analysis							
	All patients		SMN		Cumulative incidence		
	N (%)		N (%)		at 20 years (SE)		P
All	3590 (100%)		95 (100%)		5.3 (0.7)		
Sex							
Female	952 (26.5%)		40 (42.1%)		8.4 (1.7)		0.0008
Male	2638 (73.5%)		55 (57.9%)		4.0 (0.8)		
Age at diagnosis							
<5 years	663 (18.5%)		21 (22.1%)		6.1 (1.8)		0.51
5 – 10 years	1495 (41.6%)		43 (45.3%)		5.4 (1.2)		
>10 – 14 years	1432 (39.9%)		31 (32.6%)		4.6 (1.1)		
Known CPC							
Yes	57 (1.6%)		11 (11.6%)		19.9 (7.2)		<0.0001
No	3533 (98.4%)		84 (88.4%)		4.9 (0.7)		
NHL entity							
LBL	810 (21.2%)		41 (43.2%)		9.3 (1.9)		<0.0001
other	2780 (77.4%)		54 (56.8%)		3.9 (0.8)		
Stage of NHL at primary diagnosis							
I, II	1008[#] (29.0%)		17 (17.9%)		0.03 (0.01)		
III, IV	2464[#] (71.0%)		78 (82.1%)		0.1 (0.04)		0.08
Bone marrow involvement							
Positive	705 (19.6%)		22 (23.2%)		0.07 (0.02)		0.61
Negative	2885 (80.4%)		73 (76.8%)		0.05 (0.01)		
CNS status							
Positive	249[##] (7.3%)		9 (9.5%)		3.9 (1.7)		0.21
Negative	3170[##] (92.7%)		86 (90.5%)		5.4 (0.8)		
Type of therapy							
ALL-type	1120 (31.2%)		47 (49.5%)		8.7 (1.7)		0.0002
B-NHL-type	2470 (68.8%)		48 (50.5%)		3.7 (0.7)		
Anthracyclines[+]							
≤ 200mg/m² BSA	2944 (82.0%)		63 (66.3%)		4.3 (0.8)		
> 200mg/m² BSA	646 (18.0%)		32 (33.7%)		8.7 (1·8)		<0.0001
Alkylating agents[++]							
CPM ≤2 g/m²BSA	2160 (60.2%)		77 (81.1%)		0.8 (0.6)		
CPM >2g/m²BSA	1430 (39.8%)		18 (18.9%)		5.3 (2.4)		0.30
Etoposide							
≤ 800mg/m² BSA	1935* (72.0%)		39 (81.3%)		3.5 (0.7)		

> 800mg/m² BSA	753* (28.0%)		9 (18.7%)		1.6 (0.9)		0.94
Cranial radiotherapy/risk for CNS-SMN							
Yes	486[###] (13.7%)		7 (58.3%)		1.9 (0.8)		0.01
No	3066[###] (86.3%)		5 (41.7%)		0.2 (0.1)		
Radiotherapy (overall risk)							
Yes	524 (14.6%)		24 (25.3%)		4.9 (1.2)		0.86
No	3066 (85.4%)		71 (74.7%)		5.2 (0.9)		

Cumulative drug doses were calculated as per protocol
[+]Doxorubicin equivalent dose was calculated at 1:1 ratio for the used anthracyclines (doxorubicin and daunorubicin)
[++]Alkylating agents: conversion factor for cyclophosphamide equivalent dose was 1:4 (i.e. 1 mg cyclophosphamide equals 4 mg ifosfamide)
*indicates only patients receiving B-NHL-type therapy
information about stage of disease missing in 118 patients
[##] information about CNS involvement missing in 171 patients
[###] information about cranial radiotherapy missing in 38 patients
Abbreviatons: ALCL: anaplastic large-cell lymphoma; ALL: acute lymphoblastic leukemia; B-NHL: mature B-cell lymphoma; BSA: body surface area; CI: confidence interval; CNS: central nervous system; CPC: cancer-predisposing condition, CPM: Cyclophosphamide; HR: hazard ratio; LBL: lymphoblastic lymphoma; nfc: not further classified; NHL: Non-Hodgkin Lymphoma; No.: number; SE: standard error; SMN: second malignant neoplasm

Table 2. Stepwise Cox regression analysis of risk factors for the development of second malignant neoplasms (SMN) after Non-Hodgkin lymphoma (NHL) in children < 15 years of age at diagnosis, treated according to one of the consecutive NHL-BFM studies NHL-BFM-81, through EURO-LB-02/B-NHL-04.

	HR (95% CI)	P
Sex		
female vs. male	1.87 (1.23-2.86)	0.004
NHL entity		
LBL vs. other	2.6 (1.69-3.97)	<0.001
CNS involvement		
positive vs. negative	2.24 (1.03-4.88)	0.042
Known CPC		
yes vs. no	11.2 (5.52-22.75)	<0.001

Abbreviatons: CI: confidence interval; CNS: central nervous system; CPC: cancer-predisposing condition; HR: hazard ratio; LBL: lymphoblastic lymphoma; NHL: Non-Hodgkin Lymphoma

Table 3. Characteristics and outcome of patients with second malignant neoplasms (SMNs) after Non-Hodgkin Lymphoma (NHL) in children

		Second malignant neoplasm			Primary NHL				
No. of pts	Sex M/F	SMN type [no. of patients]	Latency years median (range)	Outcome: alive/death/3rd malignancy/LFU	Type of NHL [no. of patients]	Age at Dx years median (range)	Stage of disease I/II/III/IV	Therapy type ALL/B-NHL	Radio-therapy Yes/no/ unknown
21	12/9	**MDS and AML:** MDS-AML del(5),del(7) and/or complex karyotype [6] AML t(11q23) [4] AML normal karyotype [5] AML other [3] AML no cytogenetics [3]	3.1 (0.3 – 8.7)	5/14/1/2	T-LBL [9] pB-LBL [5] BL/B-AL [5] B-NHL [1] NHL nfc [1]	3.4 (0.7-14.6)	1/0/8/12	15/6	4/15/2
20	13/7	**Second lymphoid malignancy:** T-LBL [3] ALL [4] BL/B-AL [3] B-NHL [3] ALCL [1] PTCL [2] HD [4]	5.7 (1.5 – 20.2)	7/7/5/2	T-LBL [3] BL/B-AL [4] B-NHL [10] ALCL [3]	8.1 (0.7-14.9)	2/3/13/2	3/17	1/19/0
12	9/3	**CNS malignant tumors:** Glioblastoma multiforme [3] Anapl. Astrocytoma °III [3] Anapl. Meningeoma°III [3] Medulloblastoma [1] undifferentiated [2]	8.6 (0.8 - 17.3)	3/6/1/3	T-LBL [4] pB-LBL [1] BL/B-AL [2] B-NHL [3] ALCL [1] PTCL [1]	6.8 (1.9-11.3)	0/3/6/3	6/6	7/2/3
26	13/13	**Carcinoma:** Basal cell carcinoma [9] Gastrointestinal tract [9]	15.9 (0.7 – 30.3)	15/4/1/6	T-LBL [13] pB-LBL [1] BL/B-AL [4]	9.5 (1.6-13.3)	3/1/18/4	15/11	8/14/4

		Thyroid [4] Breast [1] NPC [1] Renal [1] Urothel [1]			B-NHL [1] ALCL [6] NHL n.f.c. [1]				
5	4/1	**Sarcoma:** RMA [1] Leiomyosarcoma [1] Clear cell sarcoma [1] Ewing sarcoma [1] Osteosarcoma [1]	8.6 (1.9-15.3)	3/2/0/0	T-LBL [1] BL/B-AL [2] B-NHL [1] NHL nfc[1]	5.5 (1.3-10.4)	0/2/1/2	1/4	1/4/0
4	2/2	**Malignant Melanoma**	12.3 (1.6-30.0)	3/0/0/1	T-LBL [1] BL [1] B-NHL [2]	10.5 (5.3-13.7)	0/1/2/1	1/3	1/3/0
7	2/5	**Other:** Extrarenal rhabdoid tumor [1] Seminoma [1] Malignant Phylloides [1] Desmoid-Fibromatosis [1] Hemangioendothelioma [1] LCH [1] Polycythemia rubra vera [1]	6.3 (0.2-14.7)	2/3/1/2	T-LBL [3] B-NHL [1] ALCL [3]	10.1 (0.3-13.5)	0/1/5/1	2/5	0/7/0

Abbreviations: ALCL: anaplastic large-cell lymphoma, B-NHL: mature B-cell lymphoma (other than BL/B-AL), BL/B-AL: Burkitt lymphoma /leukemia, HD: Hodgkin disease, LCH: Langenhans Cell Histiocytosis, LBL: lymphoblastic lymphoma, nfc: not further classified, NPC: nasopharyngeal carcinoma, PTCL: peripheral T-cell lymphoma, RMA: alveolary rhabdomyosarcoma

Table 4. Second malignant neoplasms (SMN) after Non-Hodgkin lymphoma in children in patients with known cancer predisposition condition

Sex	Age (years) at NHL-Dx	Predisposing condition	1. NHL	Therapy type	RT*	SMN	Latency time to SMN (years)	3. malignant neoplasm	4. malignant neoplasm	Outcome
M	1.9	Fanconi Anemia	BL	B-NHL	No	Medulloblastoma	2.1	MDS-RAEB/AML	-	Death of SMN
M	3.4	Neurofibromatosis 1	T-LBL	ALL-type	No	AML	1.8	-	-	Death of SMN
M	9.3	ID n.f.c.	ALCL	B-NHL	No	DLBCL	4.8	Osteosarcoma	T-ALL	Death of SMN
M	9.6	ID (organ transplant)	DLBCL	B-NHL	No	c-ALL	4.4	-	-	Death of SMN
F	1.3	ID (organ transplant)	NHL n.f.c.	B-NHL	No	Leiomyosarcoma	1.9	-	-	alive
F	9.5	NBS	PB	B-NHL	No	BL	3.4	T-ALL	-	Death of SMN
F	5.6	NBS	DLBCL	B-NHL	No	ALCL	3.8	-	-	Death (other)
F	9.6	CMMRD (compound heterozygote PMS2-mutation)**	DLBCL	B-NHL	No	c-ALL	2.4	Colon-CA	-	alive
F	1.2	CMMRD (mutation in the MSH2 gene)**	T-LBL	ALL-type	No	B-NHL	11.1	Phylloides-tumor;	Anaplastic astrocytoma	alive
F	6.5	CMMRD (mutation in PMS2 gene)	T-LBL	ALL-type	No	Colon-CA	9.8	Urothel-CA	-	Death of SMN
F	6.9	Gorlin-Goltz syndrome	T-LBL	ALL-type	Yes	NPC	8.8	-	-	Death (therapy related)

* 6 of the 57 patients with known cancer predisposition condition in the study cohort received radiotherapy

** CMMRD diagnosis was first made after the occurrence of SMN

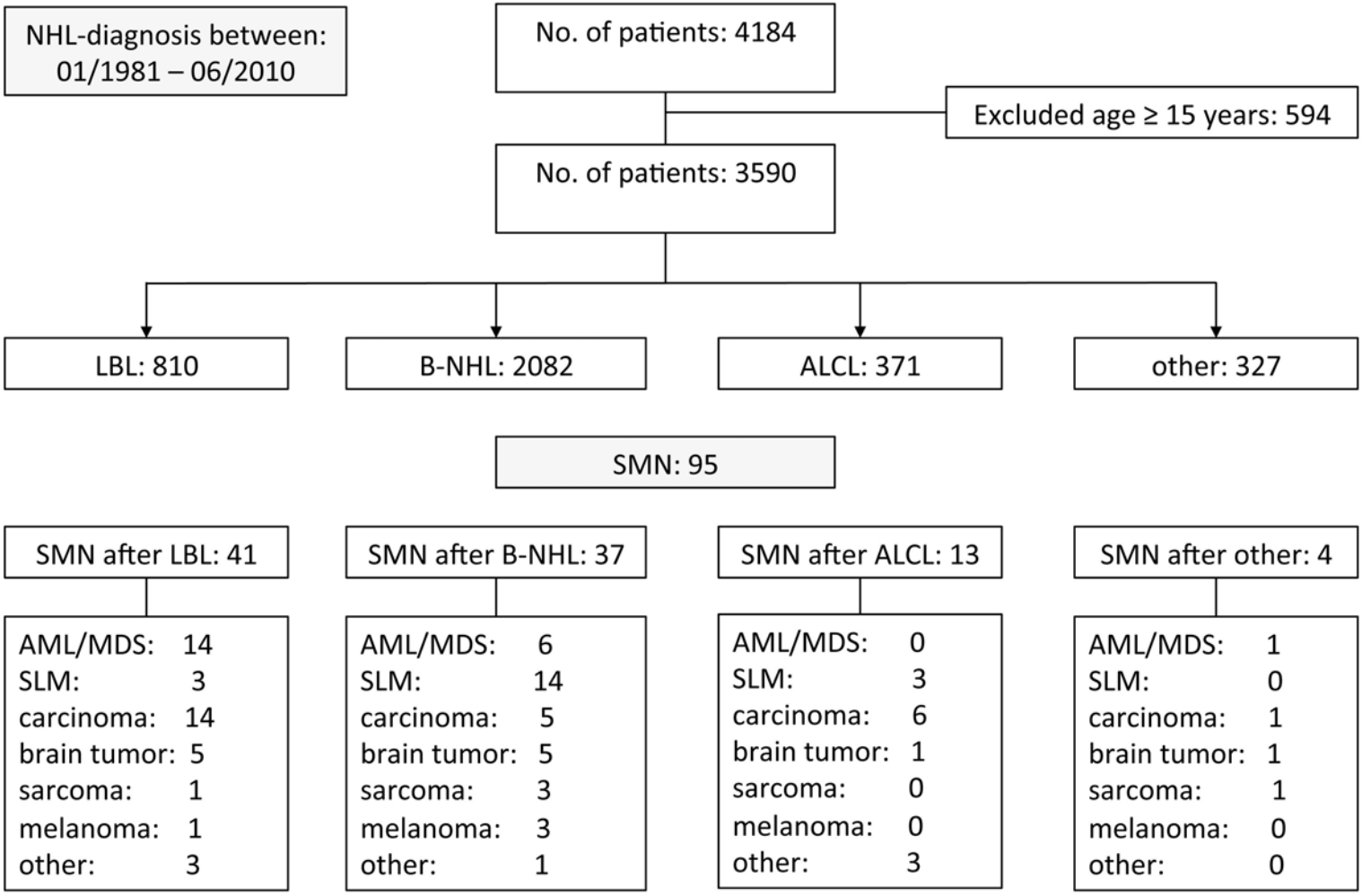
Abbreviations: ALCL: anaplastic large-cell lymphoma; BL: Burkitt lymphoma; B-NHL: mature B-cell lymphoma (other than BL/B-AL); CA: carcinoma; DLBCL: diffuse large B-cell lymphoma; CMMRD: constitutive mismatch repair deficiency syndrome, caused by mutations in DNA mismatch repair genes PMS2, MSH6, MSH2 or MLH1; CPC: cancer predisposing condition; Dx: diagnosis; F: female; ID: immune deficiency; M: male; NBS: Nijmegen breakage syndrome; n.f.c.: not further classified; NHL: Non-Hodgkin lymphoma; NPC: Nasopharyngeal carcinoma; PB: plasmoblastic lymphoma; RT: Radiotherapy; T-LBL: T-cell lymphoblastic lymphoma;

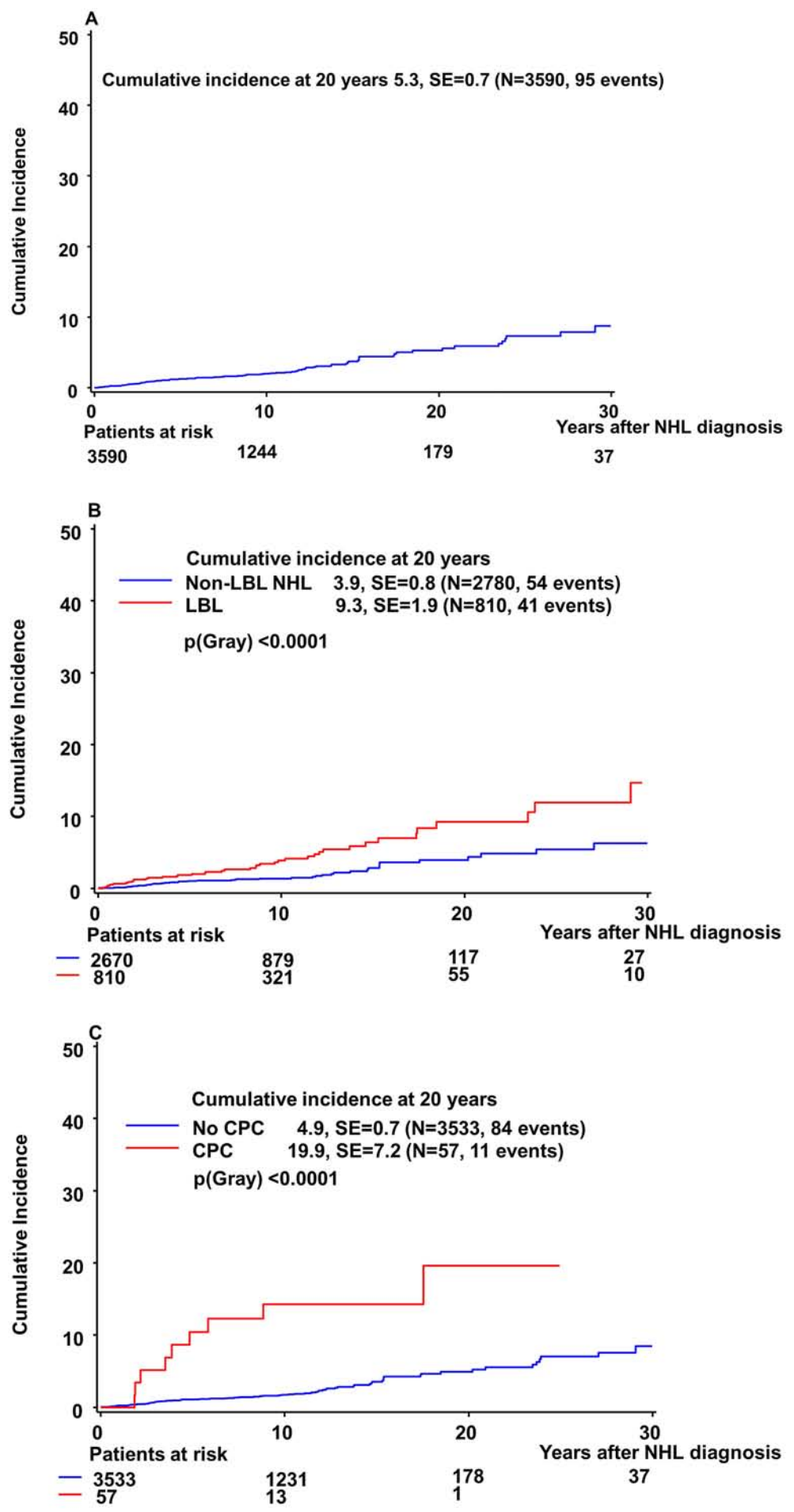
Figure legends

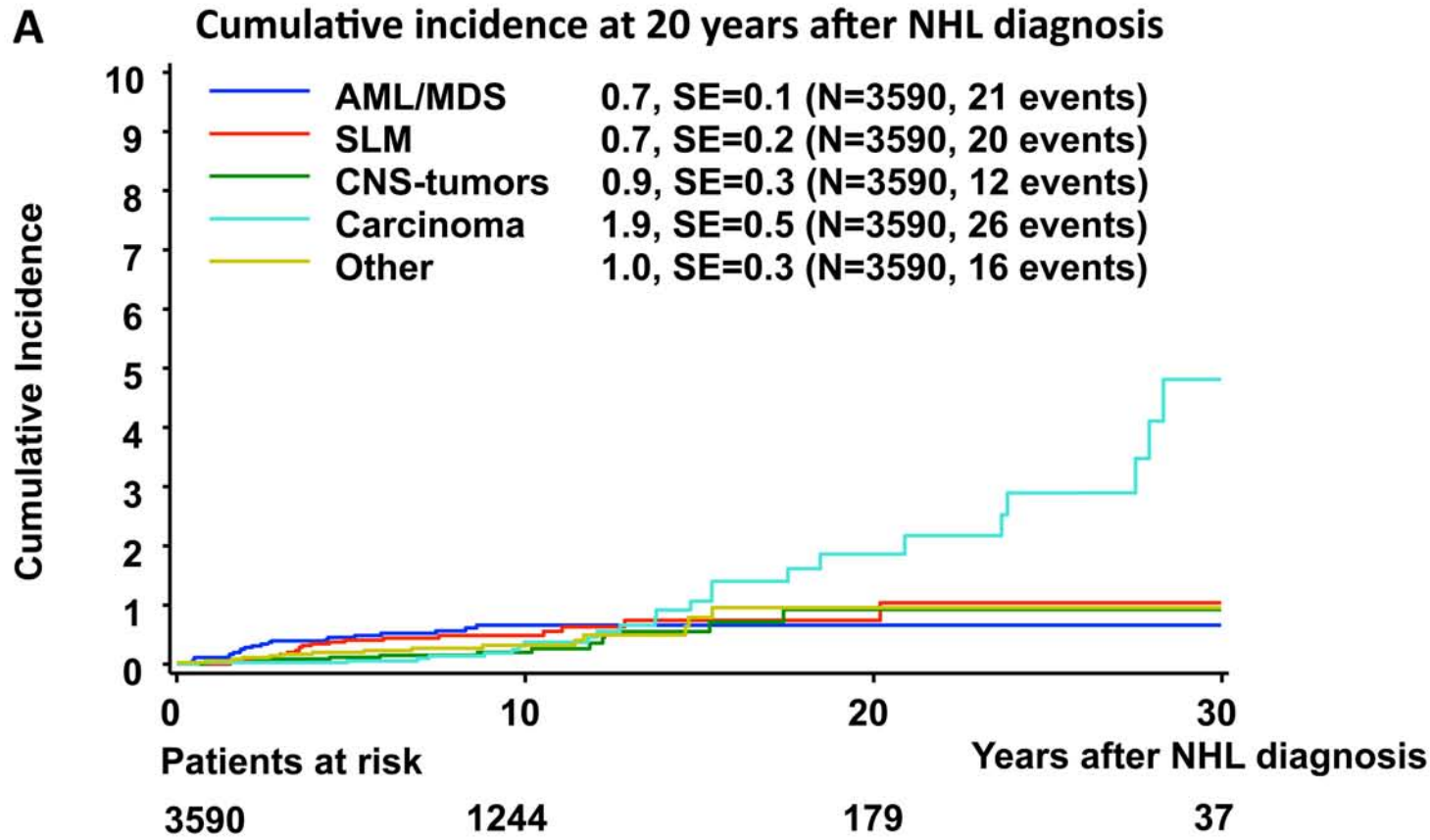
Figure 1. Consort diagram: Numbers of analyzed patients and second malignant neoplasms (SMN). Abbreviations: ALCL: anaplastic large-cell lymphoma; AML/MDS: acute myeloid leukemia/myelodysplastic syndrome; LBL: lymphoblastic lymphoma; NHL: non-Hodgkin lymphoma, No: number; SLM: second lymphoid malignancy, SMN: second malignant neoplasm

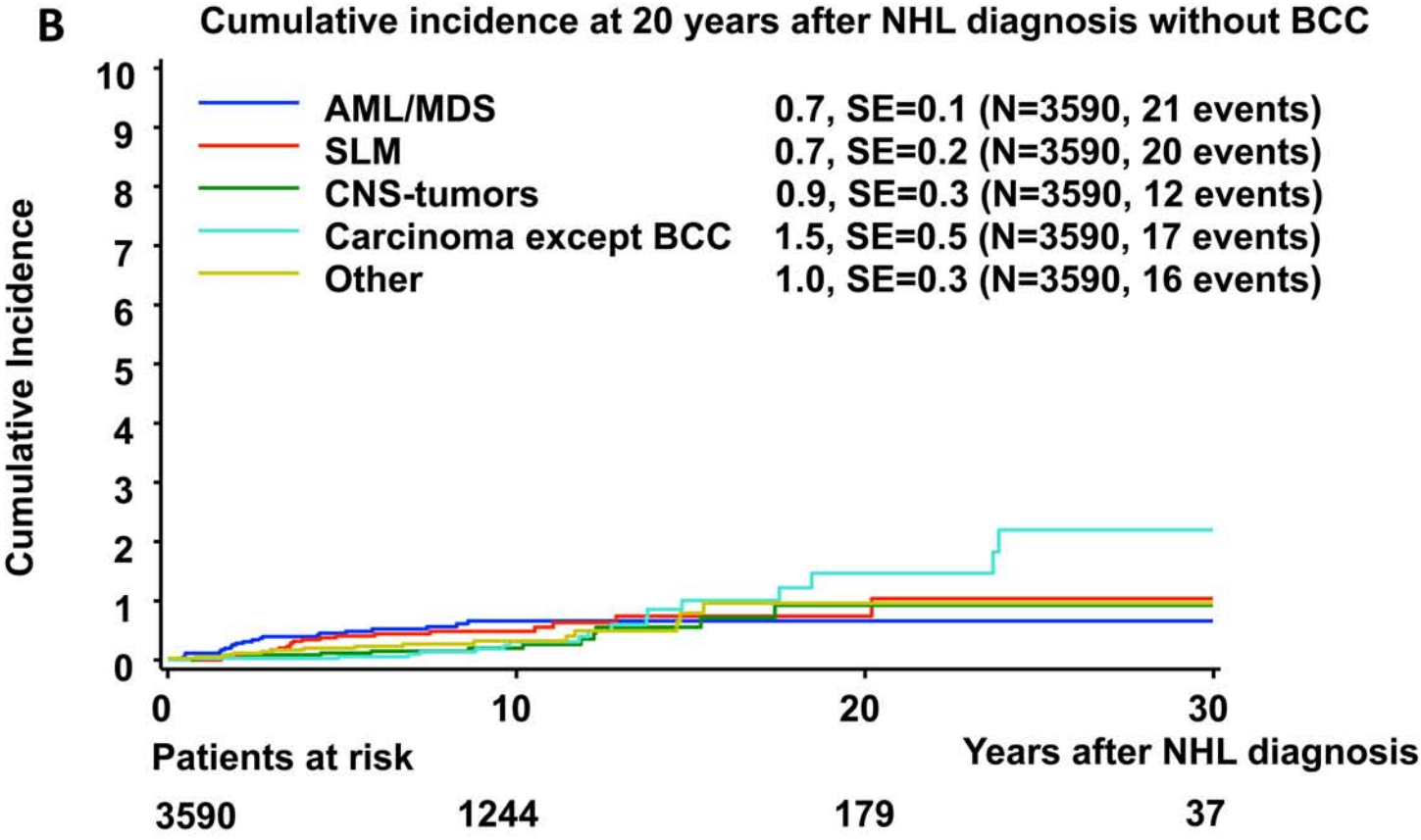
Figure 2. Estimated cumulative incidence of second malignant neoplasms (SMN) in patients with NHL <15 years of age at diagnosis, treated in one of the consecutive NHL-BFM studies NHL-BFM-81, through EURO-LB-02/B-NHL-04.
A: Cumulative incidence of SMN for all analyzed patients (5.3% ±0.7).
B: Cumulative incidence of SMN for patients with lymphoblastic lymphoma (LBL) (9.3 ±1.9), as compared to patients with other NHL (Non-LBL NHL) (CI 3.9 ±0.8).
C: Cumulative incidence of SMNs for NHL-patients with known cancer-predisposing condition (CPC) (19.9 ±7.2), as compared to patients without known CPC (4.9 ±0.7). SE: standard error

Figure 3. Estimated cumulative incidence of second malignant neoplasms (SMN) 20 years after NHL-diagnosis in 3590 NHL-patients <15 years of age, treated in one of the consecutive NHL-BFM studies NHL-BFM-81, through EURO-LB-02/B-NHL-04 according to the type of SMN. A: Cumulative incidence of all SMN, B: Cumulative incidence without basal-cell carcinoma (BCC).
Abbreviations: AML/MDS: acute myeloid leukemia/myelodysplastic syndrome; SE: standard error, SLM: second lymphoid malignancy


NHL-diagnosis between:
01/1981 – 06/2010
No. of patients: 4184
Excluded age ≥ 15 years: 594
No. of patients: 3590
LBL: 810
B-NHL: 2082
ALCL: 371
other: 327
SMN: 95
SMN after LBL: 41
AML/MDS: 14
SLM: 3
carcinoma: 14
brain tumor: 5
sarcoma: 1
melanoma: 1
other: 3
SMN after B-NHL: 37
AML/MDS: 6
SLM: 14
carcinoma: 5
brain tumor: 5
sarcoma: 3
melanoma: 3
other: 1
SMN after ALCL: 13
AML/MDS: 0
SLM: 3
carcinoma: 6
brain tumor: 1
sarcoma: 0
melanoma: 0
other: 3
SMN after other: 4
AML/MDS: 1
SLM: 0
carcinoma: 1
brain tumor: 1
sarcoma: 1
melanoma: 0
other: 0


A
Cumulative incidence at 20 years 5.3, SE=0.7 (N=3590, 95 events)
Cumulative Incidence
50
40
30
20
10
0
0
10
20
30
Years after NHL diagnosis
Patients at risk
3590
1244
179
37
B
Cumulative incidence at 20 years
Non-LBL NHL 3.9, SE=0.8 (N=2780, 54 events)
LBL 9.3, SE=1.9 (N=810, 41 events)
p(Gray) <0.0001
Cumulative Incidence
Years after NHL diagnosis
Patients at risk
2670 879 117 27
810 321 55 10
C
Cumulative incidence at 20 years
No CPC 4.9, SE=0.7 (N=3533, 84 events)
CPC 19.9, SE=7.2 (N=57, 11 events)
p(Gray) <0.0001
Cumulative Incidence
Years after NHL diagnosis
Patients at risk
3533 1231 178 37
57 13 1


A
Cumulative incidence at 20 years after NHL diagnosis
AML/MDS 0.7, SE=0.1 (N=3590, 21 events)
SLM 0.7, SE=0.2 (N=3590, 20 events)
CNS-tumors 0.9, SE=0.3 (N=3590, 12 events)
Carcinoma 1.9, SE=0.5 (N=3590, 26 events)
Other 1.0, SE=0.3 (N=3590, 16 events)
Cumulative Incidence
0 1 2 3 4 5 6 7 8 9 10
0 10 20 30
Years after NHL diagnosis
Patients at risk
3590 1244 179 37


B
Cumulative incidence at 20 years after NHL diagnosis without BCC
AML/MDS 0.7, SE=0.1 (N=3590, 21 events)
SLM 0.7, SE=0.2 (N=3590, 20 events)
CNS-tumors 0.9, SE=0.3 (N=3590, 12 events)
Carcinoma except BCC 1.5, SE=0.5 (N=3590, 17 events)
Other 1.0, SE=0.3 (N=3590, 16 events)
Cumulative Incidence
0 1 2 3 4 5 6 7 8 9 10
0 10 20 30
Years after NHL diagnosis
Patients at risk
3590 1244 179 37

Online supplemental appendix

Supplemental methods

NHL classification

NHL were classified using classifications valid at the time of diagnosis: Kiel-,[1] Revised European-American Lymphoma-,[2] and WHO-classification,[3] respectively.

Treatment in the consecutive multicentre non-Hodgkin lymphoma-Berlin-Frankfurt-Muenster (NHL-BFM)-protocols

In all protocols, patients with lymphoblastic lymphoma (LBL) received an acute lymphoblastic leukemia (ALL)-type-BFM-regimen consisting of an eight-drug induction, consolidation with methotrexate 4 x 0.5-5g/m²/24 hours intravenously, re-intensification, and oral maintenance up to two years of total therapy duration. The cumulative doses of daunorubicine/doxorubicine (equivalence ratio 1:1) and cyclophosphamide were 120-240mg/m² and 2-3g/m², respectively. Advanced stage (III and IV) patients received prophylactic cranial radiotherapy of 12-18Gy up to the trial NHL-BFM-90. Patients with LBL and CNS-involvement received cranial radiotherapy of 12-24Gy throughout the study period. Until NHL-BFM-86, patients with LBL and persisting mediastinal tumor after induction received local radiotherapy (30Gy).

Patients with mature B-cell-NHL or anaplastic large cell lymphoma (ALCL) received two to six courses of five-day block-type chemotherapy based on dexamethasone, cyclophosphamide/ifosfamide (equivalence ratio 1:4), methotrexate, doxorubicine, etoposide, cytarabine, and intrathecal methotrexate/cytarabine/prednisolone therapy. Treatment intensity was stratified according to stage and initial LDH from study NHL-BFM-90. In the R2-group the cumulative doses were 2-4g/m² for cyclophosphamide, 50-100mg/m² for doxorubicine, and 400mg/m² for etoposide, whereas in the group R3 they were 2.4-9g/m², 100-200mg/m², and 600-900mg/m², respectively. From trial NHL-BFM 86 no prophylactic/therapeutic cranial radiotherapy was applied. Local radiotherapy was not recommended for patients with mature B-NHL. All cumulative drug- and radiation doses are listed in the supplemental tables S1 and S2.

Follow-up

In all patients registered to the NHL-BFM datacentre, follow-up status after therapy was ascertained semi-annually within the first 5 years after diagnosis and annually for the following 5 years. Thereafter it was assessed every 2 years. Standardized forms including the date of the most recent contact and the status of the patient were completed by the treating institution. In addition, the NHL-BFM study centre was notified of all SMNs after NHL reported to the GCCR. The long-term follow-up of patients was ascertained by the GCCR on the basis of five-yearly inquiries. Lost to follow-up (LFU) has been defined as lack of information about a patient after two consecutive updates.

Supplemental information, including verification of the diagnosis, pathology reports, and the outcome of the patient, was obtained for all cases of SMNs. In cases of multiple second malignancies after a NHL, only the first second cancer was taken into the analysis.

Definition of SMN

Second malignant neoplasm was considered to be proven when (i) it was a non-lymphoid malignancy, (ii) in lymphoid malignancy there was a lineage change, i.e., B lineage to T lineage and vice versa, (iii) in lymphoid malignancy there was a change with respect to the

differentiation compartment, i.e., from a precursor B (or T) neoplasm to mature B (or T) neoplasm or vice versa, (iiii) in Burkitt lymphoma/Burkitt leukemia there was a MYC rearrangement at different break points between the first and the second cancer or (iiiii) in mature B-NHL there was a different immunoglobulin light-chain restriction between the first and second malignancy i.e. λ to κ or vice versa. Not included as SMNs were eight late-recurring lymphoid malignancies with different clonal rearrangements of IgH- and T-cell-receptor-genes, but no differences with respect to discriminators listed above (ii-iiiii), since clonal evolution in these cases cannot be excluded. Evaluation of clonal origin via multiplex-PCR (BIOMED-2 method[4]) was performed for all available tumor samples in cases of second lymphoid malignancy.

References supplemental appendix

1. Lennert K, Stein H, and Kaiserling E: Cytological and functional criteria for the classification of malignant lymphoma. Br J Cancer. 1975;31(Suppl 2):29-43.
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3. World Health Organization Classification of Tumours 2001. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon.
4. van Dongen JJ, Langerak AW, Bruggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia. 2003;17:2257-2317.

Supplemental tables

Supplemental Table 1: Therapy strategy and cumulative doses of drugs and radiotherapy in the NHL-BFM-studies: ALL-type therapy

Therapy trials ALL/NHL-BFM-81, -83, -86, NHL-BFM-90, -95V, -95, EURO-LB-02: therapy strategy and cumulative doses of drugs and radiotherapy																		
ALL-type therapy																		
Trial	Group	Stage	Courses	N*	Cumulative doses in mg/m² BSA (Asparaginase in IU/m² BSA)												RT dosis in Gy	
					DNR	DOX	CPM	Ifo	VCR	MTX iv	ARAC	ASP	6MP	6TG	Pred	Dex	i.th. MTX**	CRT	LRT
81	NB 1	I, II	I-CNSp-MT18	8	120	0	3000	0	6	500x4	1200	5000x21	23320	0	1680	0	x4	0	TR30
	NB 2	III, IV	I-int-III-MT18	30	120	60	2000	0	9	0	1800	+1000x4	24720	840	1680	140	x6	0	TR30
		CNS+		2						500x4							x10	30§	
83	NB L	I, II	I-int-MT18	4	120	0	3000	0	6	500x4	1200	10000x8	22620	0	1680	0	x6	0	0
	NB H	III, IV	I-int-III-MT18	58	120	60	2000	0	9	500x4	1800	10000x12	19820	840	1680	140	x8	18#	0
		CNS+															x11	30§§	0
86	NB-SRG	I, II	I-M-MT18	5	160	0	2000	0	6	5000x4	1200	10000x8	22330	0	1680	0	x7	0	TR30

	NB-RG	III, IV	I-M-II-MT18	62	160	60	3000	0	12	5000x4	1800	10000x12	19820	840	1680	210	x9	12[#]	TR30
	NB-EG	NR/PR	I-E-II-MT18	4	160	60[&]	3000	8000	12	5000x4	17800	10000x12	18395	840	4480	210	x9	18[#]	TR30
		CNS+															x13	24[§§]	
90	SRG	I, II	I-M-MT24	23	120	0	2000	0	6	5000x4	1200	10000x8	28630	0	1680	0	x9	0	0
	RG	III, IV	I-M-II-MT24	143	120	120	3000	0	12	5000x4	1800	10000x12	28630	840	1680	210	x11	12[#]	0
		CNS+		1													x13	24[§§]	
95V	SRG	I, II	I-M-MT24	3	120	0	2000	0	6	5000x4	1200	5000x8	28630	0	1680	0	x9	0	0
	RG	III, IV	I-M-II-MT24	26	120	120	3000	0	12	5000x4	1800	5000x12	28630	840	1680	210	x11	12[#]	0
		CNS+		2													x13	24[§§]	
95	SR	I, II	I-M-MT24	24	120	0	2000	0	6	5000x4	1200	5000x8	32130	0	1680	0	x9	0	0
	MR	III, IV	I-M-II-MT24	198	120	120	3000	0	12	5000x4	1800	+10000x4	28630	840	1680	210	x11	0	0
	HR	TR>30%	Ia-6xHR-II-MT24	9															
		CNS+															x13	18[§§]	

Euro-LB	Pred	I, II	I-M-MT24/18	28	120	0	2000	0	6	5000x4	1200	10000x8	32130	0	1680	0	x9	0	0
	Dexa	I, II	I-M-MT24/18	1					12						420	236			
	Pred	III, IV	I-M-II-MT24/18	154	120	120	3000	0	12	5000x4	1800	10000x12	28980	840	1680	236	x11	0	0
	Dexa	III, IV	I-M-II-MT24/18	54											420	452			
		CNS+															x13	18§§	

* information about exact assignment to respective therapy group within the ALL-type therapy missing in 43 patients

**: i.th. MTX (patients >3 years of age: 12mg, 2-3 years of age: 10mg, <2 years of age:8 mg)
§: CRT therapeutic including spinal cord
§§: CRT therapeutic without spinal cord
#: CRT prophylactic
&: additional therapy with mitoxantron 40mg/m² BSA
MT18: maintenance therapy up to 18 months total therapy duration

MT24: maintenance therapy up to 24 months total therapy duration
MT18/24: maintenance therapy up to 18 months versus 24 total therapy duration (randomized)

Abbreviations:
drugs: ARA-C: cytarabine; ASP: asparaginase; CPM: cyclophosphamide; Dex: dexamethasone; DNR: daunorubicin; DOX: doxorubicin; IFO: ifosfamide; MTX: methotrexate; Pred: prednisone; VCR: vincristine; 6MP: mercaptopurine; 6TG: thioguanine

BSA: body surface area; CRT: cranial radiotherapy; Intens: intesified if tumor residual after 2 courses; i.th.: intrathecal therapy; LRT: local radiotherapy; MT: maintenance therapy; N: number of patients; NR: not resected; R: resected; RF: risk factors; RT: radiotherapy; TR: tumor residual

Supplemental Table 2: Therapy strategy and cumulative doses of drugs and radiotherapy in the NHL-BFM-studies: B-NHL-type therapy

Therapy trials NHL-BFM-81, -83, -86, NHL-BFM-90, -95V, -95, -B04; ALCL99: therapy strategy and cumulative doses of drugs and radiotherapy																	
B-Type therapy																	
Trial	Group	Stage	Courses	N[$]	Cumulative doses in mg/m² BSA											RT dosis in Gy		
					VM26	VP16	DOX	CPM	Ifo	VCR	MTX iv	ARA-C	Pred	Dex	i.th.	CRT	LRT	OP
B-NHL																		
81	B1	I, II-R	V-1-2-1-2	21	330	0	100	5000	0	0	500x4	600	1680	0	x4*	0	30	
	B2	II-NR, III, IV, B-AL	V-1-2-1-2-1-2-1-2	61	660	0	200	9000	0	0	500x8	1200	1680	0	x8*	24[#], 30[§]	Indiv	SL
83	B-L	I, II-R	V-1-2-1	32	330	0	50	4000	0	0	500x3	600	150	150	x3*	0	TR30	
	B-H	II-NR, III, IV, B-AL	V-1-2-1-2-1-2	98	495	0	150	7000	0	0	500x6	900	150	300	x6*	24[#]		SL
	B-H/CNS	IV/B-AL, CNS+	V-1-2z-1z-2z-1z-2z	1	495	0	150	7000	0	0	500x6	900	150	300	x1*+ OM	30[§§]		SL
86	B-SR	I, II-R	V-A-B-A	40	400	0	50	2000	8000	0	500x3	1200	150	150	x3**	0	TR30	SL
	B-RG	II-NR, III	V-A-B-A-B-A-B	110	600	0	150	4000	12000	0	500x6	1800	150	300	x6**	0	TR30	SL
	B-IV/ B-AL	IV, B-AL	V-AA-BB-AA-BB-AA-BB	75	600	0	150	4000	12000	9	5000x6	1800	150	300	x12**/	24[§§]	TR30	SL
90	R1	R	V-A-B	78	0	200	50	1400	4000	0	500x2	600	0	140	x3**	0	0	

	R2	NR!	V-AA-BB-AA-BB	211	0	400	100	2400	8000	6	5000x4	1200	0	240	x9**/	0		SL
	R3	Other, no CNS+	V-AA-BB-AA-BB-AA-BB	194	0	600	150	3400	12000	9	5000x6	1800	0	340	x13**	0		SL
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz	50	0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0		SL
	Intens.		V-AA-BB-CC“-AA-BB-CC		0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**	0		
95V	R1	R	V-A-B		0	200	50	1400	4000	0	500x2	600	0	140	x3**	0	0	
	R2	NR!	V-AA-BB-AA-BB		0	400	100	2400	8000	6	5000x4	1200	0	240	x9**//	0		SL
	R3	Other, no CNS+	V-AA-BB-AA-BB-AA-BB		0	600	150	3400	12000	9	5000x6	1800	0	340	x13**	0		SL
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz		0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0		SL
95	R1	R	V-A-B	65	0	200	50	1400	4000	0	1000x2	600	0	140	x3**	0	0	
	R2	NR,I,II, III-LDH<500	V-A-B-A-B	321	0	400	100	2400	8000	6	1000x4	1200	0	240	x5**	0	0	
	R3	NR, III-LDH≥500 <1000, IV/B-AL-	V-AA-BB-CC-AA-BB““	114	0	900	100	2400	8000	7.5	5000x4	13200	0	340	x10**//	0	0	

		LDH <1000														
	R4	NR,III/IV/ B-AL-LDH≥1000	V-AA-BB-CC-AA-BB“”-CC	230	0	1400	100	2400	8000	9	5000x4	25200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-CCz-AAz-BBz“”-CCz	6	0	1400	100	2400	8000	9	5000x4	25200	0	440	OM	0	0
B04	R1	R	V-A-B	48	0	200	50	1400	4000	0	1000x2	600	0	140	x3**	0	0
	R2	NR,I,II, III-LDH<500	V-A-B-A-B	215	0	400	100	2400	8000	6	1000x4	1200	0	240	x5**	0	0
	R3	NR, III-LDH≥500 <1000, IV/B-AL-LDH <1000	V-AA-BB-CC-AA-BB“”	82	0	900	100	2400	8000	7.5	5000x4	13200	0	340	x10**//	0	0
	R4	NR,III/IV/ B-AL-LDH≥1000	V-AA-BB-CC-AA-BB“”-CC	205	0	1400	100	2400	8000	9	5000x4	25200	0	440	x11**//	0	0
	CNS+		V-AAz1-BBz1-CC-AAz2-BBz2“”-CC		0	1400	100	2400	8000	9	5000x4	25200	0	440	x14**	0	0
	PMLBL 1	LDH<500	V-A-B-A-B-A-B	8	0	600	150	3400	12000	9	1000x6	1800	0	340	x7**	0	0

	PMLBL2	LDH≥500	V-AA-BB-CC-AA-BB-CC-BB	9	0	1400	150	3400	8000	9	5000x5	25200	0	440	x13**//	0	0
ALCL																	
81-86	In B-NHL																
90	K1	I, II-R	V-A-B-A	9	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	K2	II-NR, III	V-A-B-A-B-A-B	62	0	600	150	3400	12000	9	500x6	1800	0	340	x7**	0	0
	K3	IV	V-AA-BB-CC-AA-BB-CC	21	0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz		0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0	0
95V	K1	I, II-R	V-A-B-A	1	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	K2	II-NR, III	V-A-B-A-B-A-B	9	0	600	150	3400	12000	9	500x6	1800	0	340	x7**	0	0
	K3	IV	V-AA-BB-CC-AA-BB-CC	9	0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz	1	0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0	0

95	K1	I, II-R, no RF	V-A-B-A	4	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	K2	II-NR, III, no RF	V-A-B-A-B-A-B	24	0	600	150	3400	12000	9	500x6	1800	0	340	x7**	0	0
	K3	IV or/and RF	V-AA-BB-CC-AA-BB-CC	52	0	1300	100	2400	8000	9	5000x4	17200	0	440	x11**//	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz		0	600	150	3400	1200	9	5000x6	1800	0	340	OM	0	0
										VBL							
ALCL 99	VL	I-R	V-A-B-A	22	0	400	50	1400	8000	0	500x3	1200	0	140	x4**	0	0
	SR	NR, no RF	V-A-B-A-B-A-B	56	0	600	150	3400	12000	0	500x6	1800	0	340	x7**	0	0
			V-AM-BM-AM-BM-AM-BM		0	600	150	3400	12000	0	3000x6	1800	0	340	x1**	0	0
	HR	>1RF		89													
		lung, skin, mediastinum	V-A-BV-AV-BV-AV-BV-VBL weekly=		0	600	150	3400	12000	230	500x6	1800	0	340	x7**	0	0
		liver, spleen	V-AM-BMV-AMV-BMV-AMV-BMV		0	600	150	3400	12000	230	3000x6	1800	0	340	x1**	0	0
	CNS+		V-AA-BBz-AAz-BBz-AAz-BBz	6	0	600	150	3400	12000	9	5000x6	1800	0	340	OM	0	0

$ information about exact assignment to respective therapy group within the B-type therapy missing in 48 patients

*: i.th. MTX (12mg for age >3 years, age 2-3 years: 10mg, age 1-2 years:8 mg, age <1 year: 6mg)
**: i.th. Triple (age >3 years: MTX 12mg, ARA-C 30mg, Pred 10mg; age 2-3 years: MTX 10mg, ARA-C 26mg, Pred 8mg; age 1-2years: MTX 8mg, ARA-C 20mg, Pred 6mg; age<1 year: MTX 6mg, ARA-C 16mg, Pred 4mg)
**/: i.th. Triple with half of the dosis
**//: i.th. Triple with half of the dosis in AA, BB
§: CRT therapeutic including spinal cord
§§: CRT therapeutic without spinal cord
#: CRT prophylactic
“: if vital tumor residual after 3rd therapy course subsequent ASCT
““: if vital tumor residual after 5th therapy course subsequent ASCT
=: up to 12 months duration
!: NR and only extra-abdominal or abdominal and LDH<500 U/L, no BM-, CNS- or multilocular bone involvement

Abbreviations:
drugs: ARA-C: cytarabine; ASP: asparaginase; CPM: cyclophosphamide; DEXA: dexamethasone; DNR: daunorubicin; DOX: doxorubicin; IFO: ifosfamide; MTX: methotrexate; PRED: prednisone; VBL: vinblastin; VCR: vincristine; VM26: vimentin; VP16: etoposide;

BSA: body surface area; CRT: cranial radiotherapy; Intens: intesified if tumor residual after 2 courses; HR: high risk group; LRT: local radiotherapy; NR: not resected; OM: Omaya reservoir with intraventricular therapy; OP: operation; PMLBL-1: primary mediastinal B-cell lymphoma and LDH<500 U/L; PMLBL-2: primary mediastinal B-cell lymphoma and LDH≥500 U/L; R: resected; RF: risk factors; SL: second-look operation; SR: standard risk group; TR: tumor residual; VL: very low risk group

Supplemental Table 3: Patients with second lymphoid malignancy after Non-Hodgkin lymphoma (NHL) in childhood

Patients developing second lymphoid malignancy							
Sex	Age (years) at first NHL-Dx	1.NHL	Stage of 1. NHL	SLM	Definition	Time to SLM (years)	Outcome
M	0.7	T-LBL	III	B-NHL	Lineage switch (T-B)	3.6	Death (SMN)
M	11.1	T-LBL	III	PTCL	Change in differentiation compartment (precursor-mature)	1.9	HSCT, alive
M	8.0	BL	III	T-LBL	Lineage switch (B-T)	7.6	alive
M	8.5	B-AL	IV	T-LBL	Lineage switch (B-T)	2.9	alive
F	6.7	BL	I	BL	Light chain restriction switch (K –λ)	3.5	alive
M	10.5	BL	IV	B-AL	Different breakpoint (c-myc/IgH)	2.9	Death (TRM) after allo HSCT
M*	9.6	CB	III	c-ALL	Change in differentiation compartment (mature-precursor)	4.4	Death (SMN)
F	14.7	CB	III	HD	Different histology	3.6	LFU
M	4.8	CB	II	c-ALL	Change in differentiation compartment (mature-precursor)	2.9	HSCT, alive
F*	5.6	CB	III	ALCL-T	Lineage switch (B-T)	3.8	Death (other)

F*	9.6	CB	III	c-ALL	Change in differentiation compartment (mature-precursor)	2.4	3rd MN, alive
M	1.6	CB	III	HD	Different histology	20.1	LFU
F*	9.5	PB	III	BL	Different histology	3.4	3rd MN-death
M	14.9	TCRB	II	HD	Different histology	10.5	Alive
M	5.3	BL	I	PTCL	Lineage switch (B-T)	6.0	3rd MN-alive
F	8.2	ALCL	III	ALL	Change in differentiation compartment (mature-precursor), lineage switch	1.5	Alive
M	12.0	ALCL	II	HD	Different histology, lineage switch	12.8	LFU
M*	9.3	ALCL	III	CB	Different histology, lineage switch	4.8	3rd MN-death
F*	1.2	T-LBL	III	B-NHL	Lineage switch (T-B)	11.1	3rd MN-alive
M	10.4	B-NHL nfc	III	T-LBL	Lineage switch (B-T)	3.1	Death (SMN)

* Known cancer predisposing condition

Abbreviations: ALCL: anaplastic large cell lymphoma; ALL: acute lymphoblastic leukemia; B-AL: Burkitt leukemia; BL: Burkitt lymphoma; B-NHL: mature B-cell lymphoma (other than BL/B-AL); c-ALL: common-antigen (CD10+)-acute lymphoblastic leukemia; CB: centroblastic lymphoma; Dx: diagnosis; F: female; HD: Hodgkin disease; HSCT: hematopoetic stem cell transplantation; LFU: lost to follow-up; M:male; nfc: not further classified; PB: plasmoblastic lymphoma; PTCL: peripheral T-cell lymphoma; SLM: second lymphoid malignancy; TCRB: T-cell rich B-cell lymphoma; T-LBL: T-cell lymphoblastic lymphoma; TRM: therapy-related mortality; 3rd MN: third malignant neoplasm