21 Late Effects After Treatment of Non-Hodgkin Lymphoma in Childhood and Adolescents

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21.1 Introduction

Childhood and adolescent non-Hodgkin lymphomas (NHL) are a heterogeneous group of various lymphoid neoplasms. These include all malignant lymphomas that are not classified as Hodgkin's lymphoma. NHL were a near-fatal disease until the early 1970s. Over 80% of affected children died within the first 2 years after diagnosis. This situation has changed completely as today, in modern industrial nations, more than 80% of children with NHL are cured by combination cytostatic therapy.

Lymphoblastic lymphomas are treated according to therapeutic strategies as used in acute lymphoblastic leukemia. Burkitt lymphomas and non-lymphoblastic NHL are treated with short intensive high-dose chemotherapy courses based on corticosteroids, cyclophosphamide, and methotrexate (MTX). Both therapy regimes are also effective in treatment of large-cell anaplastic lymphomas.

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Childhood NHL diseases tend to an early systemic generalization. Thus effective combination chemotherapy is the backbone of a successful treatment strategy. The risk for relapse increases with grade of spread and tumor mass which are important criteria for setting intensity and duration of therapy. Because of the high tendency for systemic spread, the treatment of the extra compartments central nervous system (CNS) and testicles has a similar importance as in the treatment of acute leukemia. A key step in the development of today's treatment concepts was the recognition that different NHL subtypes require a very different chemotherapy strategy. The distinction between lymphoblastic and non-lymphoblastic lymphomas is the most important therapeutic strategy subdivision [1]. For lymphoblastic lymphomas, therapeutic strategies of ALL based on the principle of continuous exposure to cytostatic drugs over long periods of time are an adequate treatment [2–5]. In the therapy of Burkitt-type lymphomas and other highly malignant non-lymphoblastic NHL, a strategy of short intensive chemotherapy courses with high-dose intensity based on corticosteroids, cyclophosphamide, and MTX proved more effective [2–7]. This therapy is in principle also effective in the treatment of large-cell anaplastic lymphomas [8, 9]. Internationally, a division of childhood NHL into three major therapeutic groups has prevailed:

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1. Lymphoblastic lymphomas
2. Peripheral B-cell lymphomas (B-NHL) including Burkitt lymphoma and B-ALL
3. Large-cell anaplastic lymphomas (independent of immunophenotype)

With such a stratified therapy, patients of all entities have approximately comparable chances of survival. For some numerically small subentities as peripheral T-cell lymphomas and NK-cell lymphomas, the most appropriate form of therapy is still unclear. It is noteworthy that the successes of the 1980s and 1990s were achieved with medicines already available in the 1970s. The event-free survival after 5 years increases from 61% in first NHL-BFM study to 84% in study NHL-BFM 95.

21.2 Treatment of NHL in the Past and at Present

21.2.1 First NHL-BFM Study 1975/81

In 1975 Hansjoerg Riehm initiated at Children's Hospital of Free University in West Berlin the first cooperative multicenter therapeutic study of the BFM group on childhood and adolescent NHL. From 1975 to 1981, 116 patients up to the age of 16 were included from 17 institutions in Western Germany, West Berlin, and Vienna (Austria). Due to the common lymphoid origin of NHL, the treatment strategy was based in general on childhood acute lymphoblastic leukemia (ALL) treatment protocol of the BFM group which has been effective in the treatment of children with ALL. Thus therapy in study NHL-BFM 1975/81 contained of an initial single dose of cyclophosphamide and a multidrug induction therapy for 8 weeks (protocol I) with prednisone, vincristine, daunorubicin, L-Asparaginase, cyclophosphamide, Ara-C, MTX (intrathecal), 6-mercaptopurine, and a cranial radiotherapy with 18 Gy for patients with standard risk for relapse or 24 Gy for patients with high risk for relapse; for CNS-positive patients, the dosage for cranial radiotherapy was 30 and 24 Gy for neuroaxis [2]. Additionally, patients of high-risk group received the reintensification strategy (protocol II) for 6 weeks with dexamethasone, vincristine, doxorubicin, L-Asparaginase, cyclophosphamide, Ara-C, intrathecal MTX, and 6-thioguanine. Study BFM 1975/81 was the first one which reached well results of continuous complete remission (CCR) in 61% for all patients (74% for patients with lymphoblastic NHL), but the results for B-NHL were much worse with CCR of 32%. The treatment strategy for lymphoblastic NHL is based on the elements "induction" and "reintensification" for stages III and IV which is similar to therapy of acute lymphoblastic leukemia with some modifications to minimize late effects by decreasing the dosage of radiotherapy. The therapy used in the BFM 1975/81 study was ineffective in treating patients with B-NHL. Thus a new therapy was developed for that group.

21.2.2 Study NHL-BFM 81/83: Short Pulse-Type Chemotherapy for B-NHL

Based on the results of study NHL-BFM 1975/81, the BFM group developed a new treatment regimen for patients with B-NHL in the subsequent study NHL-BFM 81/83. The therapy consisted of two alternating 5-day courses based upon dexamethasone, intermediate-dose MTX (500 mg/m^2), cyclophosphamide, and intrathecal MTX supplemented by VM26 and cytarabine in course 1 and by doxorubicine in course 2 [3]. The principles of the treatment strategy by Günter Henze, Berlin, for B-NHL were:

1. Combination of drugs with different mechanisms of action and few overlapping toxicities
2. High-dose intensity over time by keeping intervals between therapy courses as short as possible
3. Efficient CNS-directed therapy to block the strong tendency for invasion of the CNS

Dexamethasone was included because of its activity in the cerebrospinal fluid. Cyclophosphamide

had been proven to be effective as a single agent in children with Burkitt lymphoma in Africa [10]. And higher doses up to 30 mg/kg MTX in single use combined with leucovorin had been demonstrated efficacious in children with Burkitt lymphoma [11]. Pharmacologic studies showed that therapeutic levels of MTX could be achieved in the cerebrospinal fluid by systemic administration of higher doses [12] and epipodophyllotoxins had proven to be active in resistant NHL in adults [13]. The proliferation activity of Burkitt lymphoma with a cell doubling of 25 h is extremely high [14], so a principle on this course based therapy was to maintain cytotoxically active drug concentrations by means of fractionated administration or continuous infusion over a period that is long enough to impact as many lymphoma cells as possible during the vulnerable active cell cycle [6]. So in consequence the regimen of two alternating 5-day courses increased the continuous complete remission for patients with disseminated B-NHL to 67% compared to 34% in study NHL-BFM 1975/81.

21.2.3 Stratification of Treatment

The results of study NHL-BFM 1975/81 showed that stage of disease had a prognostic impact in B-NHL, so in subsequent studies, the role of stage for stratification differed between the treatment groups. In the treatment group lymphoblastic lymphoma, formerly called nonB, treatment intensity was stratified according to stage I + II versus stage III and IV since the study NHL-BFM 81/83. Patients with stages III or IV received delayed reintensification with protocol III or protocol II from starting with study NHL-BFM 86.

In therapy group B-NHL, treatment intensity was also stratified by stage. In the NHL-BFM 81/83 study, patients with stage II were subdivided into (1) the tumor was completely resected (stage II-R) or (2) not (stage II-NR). Patients with stage I and II-R received only four of the newly designed B-courses resulting in a rate for CCR of 100% [3]. In the subsequent studies for these patients, the number of therapy courses was reduced to three in study NHL-BFM 86 and only two courses in studies NHL-BFM 90 and NHL-BFM 95 without an increase of relapses [4, 15, 16]. Patients with stages II-NR, III, and IV received eight courses of the newly designed B-type therapy in study NHL-BFM 81/83 resulting in rate for continuous complete remission of 67% as described above. All in all, three parameters seemed to have significant influence on treatment outcome. That results to the subdivision into three arms of therapy intensity: bone marrow involvement, CNS involvement, and serum concentration of lactic dehydrogenase (LDH) as a parameter of tumor mass. In study NHL-BFM 86, a benefit was found for patients with NHL of stage IV and B-cell acute lymphoblastic leukemia by introducing treatment of high-dose MTX (HD-MTX; 5 g/m^2) [17]. Results of a retrospective analysis of study NHL-BFM 86 showed that patients with stage III and pretherapeutic serum LDH concentrations ≥500 U/L had a significantly worse event-free survival (43%) compared to stage III patients with LDH <500 U/L (85%). Thus in study NHL-BFM 90, LDH was used as an additional parameter for stratification of therapy intensity [15]. Since study NHL-BFM 95, stratification into four treatment arms based on stage, resection status, LDH, and CNS involvement was done. That treatment strategy provided for patients with resected disease (10% of patients) or unresected and low LDH (45% of patients) an event-free survival of >95% with only two and four therapy courses, while patients with intermediate LDH of very LDH 1000 U/L or/and CNS involvement achieved an event-free survival of >80% with five and six therapy courses [18].

21.2.4 Local Therapy

The role of local therapy changed over the period of the studies from an obligatory part of treatment to an optional role for specific patients. The initial surgery has mainly scientific reasons for asservation of appropriate tumor issue for comprehensive diagnostics. Complete resection is only beneficial for patients with localized B-NHL so they have a

favorable outcome with only 5-day chemotherapy courses. Meanwhile the outcome for patients with localized tumors is favorable with chemotherapy alone, so surgery is not required [18]. Debulking surgery for patients with large tumors has no benefit but potentially decreases the prognosis due to delay of starting treatment with chemotherapy [8].

Second-look surgery after two or three therapy courses was mandatory in studies BFM-NHL 81/83 and BFM-NHL 83/86 for patients with B-NHL and was confined to B-NHL patients with residual tumor on imaging since study BFM-NHL 86. Since study NHL-BFM 95 indication of second look surgery was reduced to B-NHL patients with residual tumors after five courses of chemotherapy [18].

In the first study BFM-NHL 1975/81, local radiotherapy was mandatory for all patients [2] and was confined to patients with incomplete response in the subsequent studies and completely canceled in study NHL-BFM 90 without increase of local relapses [4].

21.2.5 CNS Therapy and Prevention

In study NHL-BFM 1975/81, all patients received cranial radiotherapy for prevention of CNS relapses. In case of detection lymphoma cells in CNS at diagnosis, additional spinal irradiation was performed [2]. In studies NHL-BFM 83/86 and NHL-BFM 90, there was performed an intraventricular administration of MTX for CNS-positive patients by an ommaya reservoir but there was no survival benefit achieved. During the subsequent studies, irradiation of the CNS was stepwise eliminated and substituted by systemic HD-MTX combined with intrathecally administered chemotherapy without increase of CNS relapses [19]. Since study NHL-BFM 95, only CNS-positive patients up from 1 year of age with lymphoblastic lymphoma receive cranial irradiation in age-adapted dosage [20].

21.2.6 Methotrexate as a Key Drug

MTX administered by continuous infusion over 24 h combined with tetrahydrofolic acid was part of the newly designed treatment courses (by Günter Henze) which resulted in a dramatically improved outcome of patients with advanced-stage B-NHL in study NHL-BFM 81/83 [3].

In the subsequent studies, it became clear that MTX is a key drug in the treatment of B-NHL. The event-free survival increased from 50 to 75%, while the dose increased tenfold from 0.5 g/m^2 in studies NHL-BFM 81/83 and NHL-BFM 83/86 to 5 g/m^2 in study NHL-BFM 86 [17]. In contrast HD-MTX contributes to the toxicity of treatment, especially orointestinal mucositis, which increases the risk of sepsis and toxic death. Prolonging the duration of exposure to MTX increases its activity in vitro but also its clinical toxicity [21, 22]. Study NHL-BFM 95 showed that shortening the infusion time pf HD-MTX from 24 to 4 h reduced the incidence of severe mucositis [18], but in patients of higher-risk groups R3 and R4, the failure rate increased when the infusion time of MTX was reduced. By contrast, shortening the infusion time of MTX to 4 h had no adverse impact on outcome in intermediate- and low-risk groups R1 and R2. In the subsequent study B-NHL-BFM 04, the MTX regimen for patients with B-NHL was 1 g/m^2 by infusion over 4 h in risk groups R1 and R2 and 5 g/m^2 by infusion over 24 h in risk groups R3 and R4.

21.3 Late Effects After NHL Treatment

One of the treatment's consequences for childhood cancer survivors compared to the healthy control group is an increased risk for late mortality beyond 5 years after cancer diagnosis even though it was decreased over the last years due to the therapy modifications [23]. In this section the issues of late effects focused on childhood NHL survivors are described.

21.3.1 Toxicity of Substances in NHL Treatment

Substances used in treatment of NHL can cause several late effects years or even decades after finishing therapy which are:

1. Prednisone and dexamethasone: reduced bone density, osteonecrosis, and cataract,
2. Vincristine: polyneuropathy and paresthesia,
3. Daunorubicin and doxorubicin: acute myelogenous leukemia (second neoplasm) and cardiotoxicity,
4. Cyclophosphamide and ifosfamide: infertility, acute myelogenous leukemia (second neoplasm), and myelodysplastic syndrome,
5. Cytarabine: neurocognitive deficits, and reduced intelligence quotient (IQ),
6. Methotrexate: reduced bone density, neurocognitive deficits, and reduced intelligence quotient (IQ),
7. 6-mercaptopurine and 6-thioguanine: hepatic impairment and veno-occlusive disease as the result of acute toxicity

21.3.2 Summary of Late Effects

Among all childhood cancer survivors, non cancer-related mortality is the leading cause of death by approximately 30 years from cancer diagnosis. Thus survivors of childhood NHL have increased mortality rates compared to the general population. As investigated by the Childhood Cancer Survivor Study, NHL survivors are at risk for all-cause mortality [standardized mortality ratio (SMR) 4.2] and increased risk for death from subsequent malignant neoplasms (SMR 26.7), cardiac disease (SMR 6.9), and pneumonia with or without the history of splenectomy (SMR 15.4) [24].

Additionally, it is well-known that cranial radiotherapy can cause neurocognitive deficits and motor function deficits as late effects [11]. Current data about acute leukemia patients show also an increased risk of developing this issue of late effects also for those patients who received chemotherapy only [25]. Adult survivors of childhood NHL may have also impaired neurocognitive function, which is associated with lower social attainment and poor quality of life [26]. There are also signs of accelerated aging shown 25 years after NHL therapy [19]. NHL survivors have an increased risk for depression from the group of psychological diseases as well [27].

An analysis by Ehrhardt et al. which focused on childhood NHL survivors of the St. Jude Lifetime Cohort Study (SJLIFE) showed as most prevalent severe life-threatening conditions (grades 3–4) obesity (35%), hypertension (9%), impairment of executive function (13%), attention (9%), memory (4%), impaired strength (48%), flexibility (39%), muscular endurance (36%), and mobilty (36%); the most prevalent chronic conditions in the same investigation were overweight/obesity (65%), elevated fasting glucose (37%), high total cholesterol (35%), and hypertension (25%) [28].

According to an investigation by Bhakta et al. from the St Jude Lifetime Cohort Study, childhood NHL survivors experience on average 15.1 grade 1–5 and 3.9 grade 3–5 chronic health conditions per individual by 50 years of age [29]. According to that study, the diagnosis groups of late effects are auditory, infections, reproductive, neurology, muscoloskeletal, endocrine, pulmonary, gastrointestinal, ocular, hematology, renal, cardiovascular, and neoplasms.

For several years rituximab, a chimeric anti-CD20 monoclonal antibody, has led to improved response rates in the treatment of childhood B-NHL, but from the current point of view, there is no knowledge about late effects which should be investigated in future trials [30].

The reader is also referred to the Chaps. 1–17, 37–44 of this book.

Long-term follow-up of childhood NHL survivors is performed according to the recommendations of the International Guideline Harmonization Group (www.ighg.org), to the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and to the LESS study (www.nachsorge-ist-vorsorge.de) in Germany.

21.3.3 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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