Non-Hodgkin Lymphoma (NHL) – Brief Information

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Table of Content

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1. General disease information

Non-Hodgkin lymphomas (NHL) are cancerous (malignant) diseases of the *lymphatic system*. They belong to the group of malignant *lymphoma*s. „Malignant lymphoma“ literally means „malignant tumour of the lymph node“. In medical jargon, the term summarises all cancers that arise from *cell*s of the lymphatic system (lymphocytes) and that can cause lymph node swelling.

Malignant lymphomas are classified into two major groups: *Hodgkin lymphoma*, which is named after the physician and pathologist Dr. Thomas Hodgkin, and the Non-Hodgkin lymphomas (NHL). The latter include, as implied by their name, all malignant lymphomas that do not reveal the characteristics of Hodgkin lymphoma. Differentiation between these two types of lymphomas is only possible by analysing the lymphoma tissue under the microscope (histological examination).

NHL develop from malignantly transformed *lymphocytes*, a type of white blood cells (leukocytes) found in blood and lymphatic tissue. NHL can arise from every organ comprised of lymphatic tissue. Most frequently affected are the *lymph nodes*, but other organs (for example the spleen, *thymus gland*, tonsils, and the *Peyer's patches* in the small intestines) can develop NHL as well.

Very rarely, NHL are found as circumscribed tumours at a certain site of the body. They rather tend to spread from their primary site to many other organs and tissues, such as the *bone marrow*, the liver, or the *central nervous system*. Therefore, they are, as are *leukaemia*s, considered as systemic malignancies. Their biological behaviour is very similar to that of *acute lymphoblastic leukaemia* (ALL).

Almost all NHL in children and adolescents are highly malignant, meaning that they spread fast, thereby causing severe complications, which are lethal if not treated appropriately. Low-grade NHL with slow spread, as seen mostly in adults, are rather rare in childhood and adolescence.

2. Incidence

According to the German Childhood Cancer Registry in Mainz, about 145 children and adolescents younger than 18 years are newly diagnosed with Non-Hodgkin lymphoma (NHL) in Germany per year. Thus, NHL account for approximately 6,4 % of all paediatric malignancies in this age group. Also, there are B-cell leukaemias (Burkitt leukaemias), which are treated like NHL and account for about 0.5 %, meaning 10-11 reported new diagnoses per year.

NHL can develop at any age. They mostly affect children who are older than four years. Prior to the third year of age, NHL are rather rare. Boys develop the disease more than twice as often as girls. This ratio can vary, however, depending on the type of NHL.

3. Causes

The causes of Non-Hodgkin lymphomas (NHL) still have to be elucidated. It is known so far that the disease arises from the malignant transformation of cells in the *lymphatic system*, the lymphocytes, and also, that this transformation is associated with *genetic* alterations of these cells. Why these genetic alterations exist and why they cause the disease in some children, but not in others, is not known yet. Most certainly, NHL are caused by a specific combination of many factors.

Children with certain congenital diseases of the *immune system* (such as *Wiskott-Aldrich syndrome*, *Louis-Bar syndrome*) are known to have higher risk of developing a NHL. Since these (very rare) hereditary diseases are associated with a higher predisposition to develop cancer, they are also called *cancer predisposition syndrome*s. Also, acquired immune deficiencies (for example due to *HIV* infection) and intensive immunosuppressive treatments (for example in the context of an organ *transplantation* or, less frequently, a *stem cell transplantation*), are connected with a higher risk for a Non-Hodgkin Lymphoma.

Furthermore, *virus*es, *radioactive radiation*, certain chemical substances, and drugs can play a role in the development of an NHL. However, for the majority of patients, no specific risk factor has been established yet.

4. Symptoms

Highly malignant Non-Hodgkin lymphomas (NHL) are highly aggressive *tumour*s, which grow and spread fast to different body sites, thereby causing either visible tumours or other health problems (symptoms).

First sign of the disease is usually a painless swelling of one or more lymph nodes.

Lymph node swellings due to NHL can appear in the head and neck area, at arms and legs, in the armpits, the groins or at multiple sites at the same time. The disease can also arise from *lymph nodes* that cannot be seen or palpated at all, such as those in the chest or abdomen. Large lymph nodes in the abdomen may present as tummy aches, indigestion, nausea, and vomiting as well as back pain. Sometimes they can compress the intestines and cause an intestinal obstruction. If lymph nodes in the chest are affected, for example in the so-called *mediastinum*, which is the space between the lungs, the resulting pressure on airways and lungs can lead to cough and breathing difficulty. Similar symptoms occur if the *thymus gland*, lungs, and upper airways are affected.

Frequently, other lymphatic and non-lymphatic organs and tissues are involved as well. For example, spleen and liver may be enlarged due to the infiltration by lymphoma cells (splenomegaly, hepatomegaly). Also, the membranous coverings of the brain and spinal cord (*meninges*) can be affected in patients with NHL; as a consequence, headaches, facial weakness, visual deficits, and/or vomiting may occur. Infiltration of bony tissue can cause musculoskeletal pain.

In some patients, the number of healthy white blood cells is reduced; these patients are therefore prone to infections. In case of extensive *bone marrow* infiltration, red blood cell and/or platelet count(s) can be low as well. Lack of red blood cells leads to *anaemia*, whereas a lack of platelets can present as pinpoint round spots on the skin (petechiae) caused by bleeding.

Aside from above *symptom*s, patients may experience more general signs of illness, such as fever, unintended weight loss, night sweats, and fatigue. Three of these frequently occur together in patients with NHL: fever (higher than 38°C), drenching night sweats, and unintended weight loss of more than 10 % over the last six months. This combination of symptoms is also known as the *B-symptoms*.

The following overview summarizes the most frequent symptoms caused by Non-Hodgkin lymphoma.

4.1. General symptoms

- fever of unknown origin (over 38°C, persisting or recurrent) [B-symptom]
- night sweats [B-symptom]
- unexplained weight loss (more than 10 % in six consecutive months prior to admission) [B-symptom]
- fatigue, listlessness, loss of appetite, malaise

4.2. Specific symptoms

- painless, palpable packages of swollen *lymph nodes*, for example in the area of the head or neck, in the armpits or groins
- abdominal pain, diarrhea or constipation, vomiting and loss of appetite (if abdominal lymph nodes or organs, such as liver or spleen, are involved)
- chronic cough, shortness of breath (if thoracic lymph nodes, *thymus gland*, lungs or respiratory tract are involved)
- bone or joint pain (if bones are involved)
- headache, visual disturbances, vomiting (also on an empty stomach), cranial nerve palsies (due to involvement of the *central nervous system*)
- increased risk of infections due to lack of functional white blood cells
- pallor due to lack of red blood cells (anaemia; if the bone marrow is involved)
- pinpoint, round and red spots on the skin (*petechiae*) caused by an increased risk of bleeding due to lack of platelets

Good to know: Symptoms and complaints usually develop within a few weeks. They can vary individually with regards to type and intensity. However, the occurrence of one or more of the above-mentioned symptoms does not necessarily mean that they are caused by an NHL. Several of these symptoms, such as lymph node swelling and fever, are exactly those often seen with common childhood diseases like colds and other viral *infection*s. Nevertheless, it is strongly recommended to have the child or teenager see a paediatrician, in particular, if symptoms persist or progress.

5. Diagnosis

If the paediatrician thinks that the young patient's history (*anamnesis*) *physical examination* and possibly even results from blood tests, *ultrasound* and/or *X-ray examination* (radiographs) are suspicious of Non-Hodgkin lymphoma (NHL), the child should be referred to a hospital with a childhood cancer program (paediatric oncology program). If an NHL is suspected, a wide range of diagnostic tests is required not only to confirm the diagnosis, but also to assess the type of NHL and its extent of potential spread.

5.1. Obtaining a tumour sample (biopsy)

Two major procedures help confirming the diagnosis of an NHL: in case of excess liquid in the abdomen (ascites) or in the chest (pleural effusion), abdominal or pleural tapping are performed by needle aspiration for drainage and further fluid analysis, thereby bypassing a surgical procedure. In any case, a bone marrow specimen will be obtained, usually by *bone marrow puncture*, to check if there is any bone marrow involvement and if so, to which extent. If the bone marrow contains 25 % of lymphoblasts or more, the disease is classified as acute lymphoblastic B-cell leukaemia and will be treated as per assigned protocols. If no ascites, pleural effusion or bone marrow infiltration are found, affected *lymph nodes* or other affected tissue will be surgically removed for further analysis.

The tissue samples obtained by needle aspiration, bone marrow puncture, or surgery are analysed using *cytological*, *immunohistochemical*, *immunological*, and *genetic* methods in the laboratory. These analyses allow precise assessment of the patient's type of NHL. This is a major precondition for targeted treatment planning, since the various forms of NHL do not only differ with regard to their cellular and *molecular* characteristics, but are also associated with different courses of the disease, outcomes, and responses to treatment.

5.2. Tests to assess spread of the disease

Once the diagnosis of Non-Hodgkin lymphoma has been confirmed, further tests are required to find out if and to which extent the cancer has spread and which organs are involved. These tests include *imaging*, such as ultrasound and radiographs, *magnetic resonance imaging* (MRI), and/or *computed tomography* (CT). MRI and CT imaging are more and more routinely combined with *positron emission tomography* (PET scan), which helps detect lively, metabolising lymphoma tissue very effectively (so-called PET-MRI or PET-CT, respectively).

To evaluate potential central nervous system (CNS) involvement, *cerebrospinal fluid* (CSF) is obtained by *lumbar puncture* for further analysis. In addition, all patients undergo a *bone marrow puncture* to assess potential bone marrow involvement.

5.3. Tests before treatment begins

For treatment preparation, tests on the patient's cardiac function (*electrocardiography* and *echocardiography*) are performed. Furthermore, additional blood tests are needed to assess the patient's general health condition and to check whether the function of certain organs (such as liver and kidneys) is affected by the disease and whether there are any metabolic disorders or infections to be considered prior or during therapy. Any changes occurring during the course of treatment can be assessed and managed better based on the results of those initial tests, which thus help to keep the risk of certain treatment-related side effects as low as possible. Also, the patient's *blood group* needs to be determined in case a *blood transfusion* is required during treatment.

Good to know: Not all the tests listed above need to be done for every patient. Contrariwise, the patient's individual situation may require additional diagnostic procedures that have not been mentioned in this chapter. You should, therefore, always ask your doctor, based on the information above, which test your child needs and why.

6. Treatment planning

After having confirmed the diagnosis of a Non-Hodgkin lymphoma (NHL), the doctors will plan the treatment. In order to provide a therapy that is specifically designed for the patient's individual situation (risk-adapted therapy), the doctors will take into consideration certain factors that have been shown to have an impact on the *prognosis* (so-called risk factors or prognostic factors).

Relevant *prognostic factors* and, thus, important criteria for NHL treatment are:

- the type of NHL: it determines the protocol as per which the patient should be treated
- the extent / potential spread (stage) of the disease: it determines the intensity and duration of the treatment

The following information gives an overview on the different types and stages of NHL.

6.1. Types of Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHL) are classified into different subgroups based on certain characteristics. The international *WHO classification* differentiates between the following three major subgroups of NHL:

Aside from these three major subtypes, which are partially further differentiated, there are more, rare forms of NHL.

- **Precursor B-cell and Precursor T-cell lymphoblastic lymphomas (B-LBL, T-LBL):** these arise from immature precursors of *B lymphocytes* and *T lymphocytes* and are therefore closely

related to the acute lymphoblastic leukaemia (ALL). In Germany, they account for about 25-30 % of childhood NHL.

- **Mature B-cell lymphomas and mature B-ALL:** these develop from mature B-cells and comprise about 50-60 % of childhood NHL, thereby representing the most frequent NHL subtype in children and adolescents in Germany. Most frequent B-cell lymphomas are Burkitt lymphoma and the mature B-ALL.
- **Mature T-cell lymphomas such as anaplastic large cell lymphomas (ALCL):** these arise from mature T lymphocytes and account for about 10-15 % of all childhood NHL.

Aside from these three major subtypes, which are partially further differentiated, there are more, rare forms of NHL.

Good to know: The different NHL subtypes vary a lot with regard to the course and the outcome (prognosis) of the disease. Therefore, patients are assigned to three different treatment groups with different treatment plans, based on the NHL subtype that has been diagnosed. Hence, correct classification of NHL is crucial for choosing the right treatment.

6.2. Stages of Non-Hodgkin Lymphoma

Staging of Non-Hodgkin lymphoma is crucial for both treatment planning and estimating prognosis. The stage of the disease is primarily assessed based on its spread at the time of initial diagnosis. It describes which lymph node regions, organs, and tissues of the body are involved and to which extent. The staging of some NHL (such as the large cell anaplastic lymphoma) also takes into consideration whether or not the patient has been experiencing *B-symptoms* (*please see also chapter "Symptoms"*).

The most frequently applied staging system has, until recently, been the St. Jude's staging classification for childhood NHL (Murphy staging system). In 2015, this staging system was replaced by the so-called “International Paediatric Non-Hodgkin Lymphoma Staging System" (IPNHLSS), which represents an extension and a more detailed version of the previous classification.

The IPNHLSS classification differentiates between four stages of disease (I-IV): Stage I corresponds to a single tumour inside or outside a lymph node (e.g. in the skin or bones), but not in the chest or abdomen. In stages II and III, more than one lymph node or other tissue/organ (including in the abdomen or chest) are affected. In addition to the possible tumour manifestations mentioned above, the most advanced stage of the disease (stage IV) is also characterised by an involvement of the *central nervous system* and/or *bone marrow*.

***Note to Stage IV:** Lymphoblastic lymphomas revealing 25 % of bone marrow infiltration or more are not defined as NHL, but as acute lymphoblastic leukaemia (ALL). Lymphoblastic lymphomas and ALL are biologically closely related, since they all arise from B- or T-cell precursors. Mature B-cell/Burkitt lymphomas presenting with 25 % of bone marrow involvement or more are known as Burkitt leukaemias, which represent a more advanced stage of the same disease, NOT a form of ALL. Patients with Burkitt leukaemia are treated as NHL patients.

7. Treatment

Treatment of children and adolescents with Non-Hodgkin lymphoma should take place in a children's hospital with a paediatric oncology program. Only such a treatment centre provides highly experienced and qualified staff (doctors, nurses, and many more) that is specialised and focussed on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised. The goal of the treatment is to achieve high cure rates while avoiding acute or long-term side effects as much as possible.

7.1. Treatment methods

Central backbone of treatment for patients with NHL is always **chemotherapy**. It uses drugs (so-called cytostatic agents) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. Since one cytostatic agent alone may not be capable of destroying all the lymphoma cells, a combination of *cytostatics* that function in different ways is given (polychemotherapy). The goal is to eliminate as many malignant cells as possible. In addition to *chemotherapy*, some few patients may also receive **radiotherapy** (for example *radiation therapy* of the brain) to increase the success of treatment.

Since NHL are so-called *systemic* diseases that affect the whole organism, *surgery* is usually not a feasible treatment option. It is only recommended for diagnostic reasons, such as removal of an affected lymph node for further analysis. In case of small tumours, this strategy can be used therapeutically, that means for complete tumour resection, too. Hence, a less intensive chemotherapy regimen may be sufficient in those patients. Completely sparing chemotherapy, however, is a very rare option (for example in patients with isolated skin involvement).

In certain situations, for example if the disease does not respond to standard therapy or in case of recurrent disease (relapse), **high-dose chemotherapy** may be necessary. The high doses of cytostatics given according to this treatment strategy are capable of eliminating even resistant lymphoma cells. Since *high-dose chemotherapy* also leads to the destruction of the blood-forming cells in the *bone marrow*, the patient will receive blood-forming stem cells in a second step. Usually, these *blood stem cells* are obtained from the bone marrow of a donor (*allogeneic stem cell transplantation*) or from the patient (*autologous stem cell transplantation*). Other treatment strategies (such as *antibody* therapy) are currently tested in the framework of different clinical trials.

Intensity and duration of chemotherapy, necessity of radiotherapy or stem cell transplant as well as the *prognosis* of the disease are primarily determined by the subtype of NHL, the extent of the disease at the time point of diagnosis (stage) and how the disease responds to therapy (*see chapter "Treatment planning"*)

7.2. Course of treatment

Patients with Non-Hodgkin lymphoma (NHL) receive treatment according to various treatment protocols, which provide for different courses of therapy, depending on the subtype of NHL. All these protocols have in common that treatment, mostly chemotherapy, consists of multiple phases of therapy, which not only vary regarding their duration, but also the combination of chemotherapy, the intensity, as well as the goal of treatment. The treatment plans take into consideration the subtype of lymphoma, the extent of the disease, and additional factors (such as the affected anatomic sites), which represent every patient's individual situation.

The chemotherapeutic agents are usually given *intravenous*ly, as an *infusion* or *injection*, some are given *oral*ly as well. That way they get distributed in the blood system and can, thus, eliminate lymphoma cells throughout the whole body (systemic chemotherapy). In addition to this approach, some chemotherapy is given directly into the cerebrovascular fluid, which surrounds both brain and spinal cord (*intrathecal chemotherapy*). This is necessary because most chemotherapeutic agents cannot pass the barrier between blood and brain (*blood-brain barrier*).

The following paragraph will introduce the treatment plans for the three major NHL subtypes as per treatment recommendations of the current NHL-BFM registry 2012 (*see chapter "Therapy optimizing trials and registries"*). Please note that patients who are treated within trials may receive therapies other than the standard treatments described below. The studies are the current treatment standard in paediatric oncology.

7.2.1. Precursor B-cell and T-cell lymphoblastic NHL (LBL)

For patients with lymphoblastic lymphoma, a strategy containing multiple treatment phases (similar to treatment of *acute lymphoblastic leukaemia*, ALL), has proven to be a successful approach. The **overall treatment duration** takes about two years, unless the patient experiences progressive disease during treatment or relapse after cessation of therapy.

Important elements of treatment are:

1. **Pretreatment**: The *cytoreductive* pre-phase is part of induction therapy. It serves the initiation of therapy and consists of a brief (about a week) *chemotherapy* with one or two different agents given *intravenous*ly or in tablets (*oral*ly). In order to also reach lymphoma cells in the central nervous system, another agent is given directly into the spinal canal (*intrathecal chemotherapy*, *see section "CNS therapy" below*). The goal of this pretreatment is to stepwise (and, thus, gently for the organism) reduce the initial burden of lymphoma cells, in order to prevent complications, such as *tumour lysis syndrome*.

2. **Induction therapy** (protokoll I): The actual induction therapy involves a very intensive chemotherapy that includes multiple agents. In its first phase (protocol Ia), which takes about a month, it aims at eliminating as many lymphoma cells as possible and, thus, at achieving *remission*. The second phase of induction (protocol Ib) is supposed to destroy still remaining lymphoma cells, thereby minimising the risk of relapse, by using a different combination of chemotherapeutic agents. This phase also takes about four weeks. Similar to the ALL treatment regimen, protocol Ib is also known as **consolidation therapy**.

3. **Protocol M**: Induction therapy is followed by a treatment phase that belongs to the extracompartment therapy (*see below*). It takes about two months and serves the treatment of the central nervous system and the testes. Depending on the stage of the disease, patients are then assigned to different treatment arms (such as maintenance therapy or reinduction followed by maintenance therapy, *see subsequent section*).

4. **Reinduction therapy** (protocol IIa/b): Only patients with advanced stages of the disease (stage III or IV) will receive reinduction therapy. However, these patients represent the majority of patients with lymphoblastic NHL. (Patients with a very low risk of developing relapse will be assigned to the maintenance arm directly, *see below*.) The intensity of reinduction therapy is similar to that of induction therapy, which means that different combinations of chemotherapy are given with high dosages. The reinduction phase takes about seven weeks and serves to make sure that all lymphoma cells have been eliminated.

5. **CNS therapy (extracompartment therapy)**: An important part of the intensive treatment (consisting of pretreatment, induction, and reinduction) as well as of protocol M is the prophylactic or therapeutic treatment of the *central nervous system* (CNS). This extracompartment treatment aims at preventing lymphoma cells from settling in the *brain* and/or *spinal cord* or from spreading further within the CNS. CNS treatment usually involves multiple applications of CNS-feasible chemotherapy given into the spinal canal (*intrathecal chemotherapy*). If the CNS is involved in the disease already at diagnosis of the NHL, patients will also receive craniospinal radiation after the intensive chemotherapy phase. The duration of radiotherapy usually takes two to three weeks depending on the radiation dose. Children under one year of age do not receive craniospinal *radiation therapy*.

6. **Maintenance therapy:** This last phase of treatment is designed to eliminate all the leukaemia cells that may not be detectable but still have survived the intensive treatment. The intensity of chemotherapy is much less than in the other phases. Also, the patient is mainly *outpatient* and may even continue with kindergarten or school. This phase of treatment is usually continued until a total treatment time of two years has been achieved.

Chemotherapy given for treatment of lymphoblastic NHL includes for example prednisone (PRED), vincristine (VCR), daunorubicin (DNR), E.-coli Asparaginase (ASP), cyclophosphamide (CPM), cytarabine (ARA-C), 6-thioguanine (6-GT), methotrexate (MTX), 6-mercaptopurine (6-MP), and dexamethasone (DEXA).

Note regarding treatment protocol LBL 2018: One goal of therapy optimising study LBL 2018 is to find out whether a different approach during induction (protocol 1a) may help reduce the development of recurrent disease with CNS involvement. In addition, the study is designed to evaluate whether an intensified treatment instead of standard therapy as per protocol 1b and protocol M will result in an increased relapse-free (event-free) survival of high-risk patients (*see chapter "Therapy optimising trials and registries"*).

7.2.2. Mature B-cell Non-Hodgkin lymphoma (B-NHL) and acute B-cell leukaemia (B-AL)

The intensity of the treatment of mature B-cell NHL or acute B-cell leukaemia primarily depends on the stage of the disease and the initial burden of lymphoma cells. This burden (tumour mass) can be estimated well based upon the concentration of a specific *enzyme* in the serum (*lactate dehydrogenase*, LDH). Furthermore, treatment intensity is based upon whether a tumor could or could not be completely removed surgically. The **entire duration of treatment** usually takes between six weeks and six months, unless there is progressive or recurrent disease, respectively.

Important elements of treatment are:

1. **Pretreatment** (*cytoreductive* pre-phase): It consists of a short (approximately five days long) phase of *chemotherapy* using moderate dosages of two different agents, which are given *intravenous*ly or in tablets (orally). In order to also reach lymphoma cells in the *central nervous system* (CNS), one or two additional chemotherapy applications are given directly into the spinal canal (intrathecal). The goal of this pretreatment is to stepwise and, thus, gently reduce the initial burden of lymphoma cells in order to prevent complications, such as *tumour lysis syndrome*.

2. **Intensive treatment**: It consists of two to six intensive chemotherapy courses, each of which takes about five or six days, followed by an approximate three weeks' break of recovery. Chemotherapy includes multiple agents given intravenously, orally and also *intrathecal*ly. The goal is to eliminate as many lymphoma cells as possible with every single course. For patients after complete tumor removal, two courses of therapy are sufficient, all other patients require at least four courses in addition to the pre-phase. Patients with CNS involvement receive an intensified *intrathecal chemotherapy*. The duration of this phase usually takes between six weeks and six months, unless there is progressive or recurrent disease, respectively.

Chemotherapy given for treatment of these NHL subtypes includes for example dexamethasone (DEXA), cyclophosphamide (CPM), methotrexate (MTX), cytarabine (ARA-C), ifosfamide (IFO), etoposide (VP-16), doxorubicin (DOX), vincristine (VCR), vindesine (VDS) und prednisone (PRED).

Note to protocol B-NHL 2013: The therapy optimising study B-NHL 2013 is currently investigating whether the established combination chemotherapy regimen can be further improved by giving the antibody rituximab (*see chapter "Therapy optimising trials and registries"*). Rituximab is a synthetical (recombinant) antibody [see *monoclonal antibodies* , which specifically binds to the surface pattern of the *B lymphocytes* (the so-called CD20-*antigen*), thereby inducing cell death.

7.2.3. Anaplastic large cell lymphoma (ALCL)

The type of treatment depends on the treatment group to which the patient has been assigned, based primarily on which organs and tissues are affected. Also, the potential complete removal of a lymphoma by diagnostic surgery is considered, however, this is only an option for a small number of patients. Patients with isolated skin involvement (rare) initially don't receive *chemotherapy*. The **overall duration of therapy** usually takes between ten weeks (for patients with stage I and after complete tumour removal) and five months, unless there is progressive or recurrent disease.

Important elements of treatment are:

1. **Pretreatment** (*cytoreductive* pre-phase): It serves as the initiation of treatment and consists of a brief (usually five days) chemotherapy with two agents that are given *intravenous*ly and *oral*ly. In order to also reach lymphoma cells in the *central nervous system*, another agent is given directly into the spinal canal (*intrathecal chemotherapy*). The goal of this pretreatment is to stepwise and, thus, genlty reduce the initial burden of lymphoma cells in order to prevent complications, such as *tumour lysis syndrome*.

2. **Intensive therapy**: It consists of three or six intensive courses of chemotherapy, each of which takes about five days and is followed by a short break of recovery. Patients with stage I disease receive three courses of chemotherapy, if complete removal of the tumor tissue was possible. All other patients receive six cycles of chemotherapy. Each cycle includes several different agents, some of which are given *systemic*ally (intravenously) and others orally. The goal is to eliminate as many lymphoma cells as possible with every single course. Patients with CNS involvement (very rare) also receive cranial *radiation therapy*.

Chemotherapy for treatment of ALCL includes dexamethasone (DEXA), cyclophosphamide (CPM), methotrexate (MTX), cytarabine (ARA-C), prednisone (PRED), ifosfamide (IFO), etoposide (VP-16), doxorubicin (DOX), and sometimes vindesine as well (VDS).

Note regarding trial ALCL-VBL: the current therapy optimising study ALCL-VBL 2018 examines whether outpatient vinblastine treatment of patients with standard risk ALCL will achieve as favourable results as the current polychemotherapy regimen. Precondition for such a treatment is that there are no remaining circulating lymphoma cells on a submicroscopic level (using sensitive diagnostics), thus having ruled out minimal disseminated disease. This is the case for about 40 % of the patients (*see also chapter "Therapy optimising trials and registries"*).

8. Therapy optimising trials and registries

In Germany, treatment of almost all children and adolescents with Non-Hodgkin lymphoma is performed according to the treatment plans (protocols) of therapy optimising trials or registries. The term "*therapy optimising trial*" refers to a form of controlled clinical trial that aims at improving current treatment concepts for sick patients based on the current scientific knowledge. With many treatment centres being involved in this kind of standardised treatment, such studies are also called "multicentred" and "cooperative", and most often many countries participate.

Patients who cannot participate in any study, for example because none is available or open for them at that time, or since they do not meet the required inclusion criteria, respectively, are often included in a so-called **registry**. To ensure optimal treatment for patients not registered in a study, therapy is following the recommendations and advice of the treatment centre.

The following trials and registries for treatment of children and adolescents with Non-Hodging lymphoma are currently active in Germany (with international participation):

- **NHL-BFM Registry 2012:** international registry of the BFM study group for all children and adolescents with a newly diagnosed NHL, regardless of the subtype (BFM is the abbreviation for the cities Berlin, Frankfurt and Münster, where these treatment protocols have been designed initially). In mid 2012, the registry was opened after cessation of various therapy trials / registries with the goal to provide optimal treatment recommendations for NHL patients even in times without an active trial. A registry does not introduce new treatment strategies; it rather recommends the currently best available and optimal therapy based on preceding trials and the international literature for patients who have not been recruited to any trial.

- **Trial B-NHL 2013:** international therapy optimising trial for patients (under 18 years of age) with a mature B-cell lymphoma or mature B-cell leukaemia. The trial was opened in August 2017 and is conducted by the NHL-BFM study group and the Scandinavian study group (NOPH). Multiple childrens' hospitals and paediatric oncology programs in Germany, Austria, Switzerland, and the Czech Republic, as well as in Denmark, Finland, Norway, and Sweden are participating. Goal of the trial is to improve the relapse-free (event-free) survival of the patients and a more rapid recovery of the *immune system* after cessation of therapy. Children with clearly localized disease (risk groups R1 and R2, stages I-II), are being assessed regarding the option of replacing previous chemotherapy with *anthracyclines* by a treatment with the anti-CD20 antibody rituximab *see chapter "Course of treatment – mature B"*.

- **Trial LBL 2018:** international therapy optimising trial of the NHL-BFM study group for patients under 18 years with a newly diagnosed lymphoblastic lymphoma. The trial was opened in September 2019, and multiple treatment centres in Germany as well as other European and additional countries are participating. One major goal is to reduce the risk of relapse (in high-risk patients by treatment intensification) and increase the probability of event-free survival for children and adolescents with lymphoblastic lymphoma.

- **Trial ALCL-VBL:** international therapy optimising study for patients (younger than 18 years of age) with newly diagnosed anaplastic large cell lymphoma (ALCL). Eligible patients present with standard risk ALCL (ALCL stage I-III without minimal disseminated disease; *see also chapter "Course of treatment – ALCL"*). The study has been open in Germany since 2021 and is currently starting in all European as well as other non-European countries. Goal of the study is to find out whether children treated by outpatient vinblastine therapy fare as well as patients receiving standard polychemotherapy.

The registry is under supervision of Prof. Dr. med. Birgit Burkhardt (Universitätsklinikum Münster) and Prof. Dr. med. Wilhelm Wößmann (Universitätsklinikum Hamburg-Eppendorf). Principal Investigator for the trials LBL 2018 and B-NHL 2013 is Prof. Dr. med. Birgit Burkhardt (Münster), for the trial ALCL-VBL Prof. Dr. med. Wilhelm Wößmann (Hamburg).

9. Prognosis

The chances of cure (prognosis) for children and adolescents with newly diagnosed Non-Hodgkin lymphoma (NHL) have significantly improved due to the immense progress in diagnosis and treatment over the last four decades. Today's modern diagnostic procedures and the use of intensive, standardised polychemotherapy protocols have resulted in long-term survival of the majority of children and adolescents with NHL (the 5- to 10-year survival rate is currently at about 90 %).

The *prognosis* for the individual patient primarily depends on the subtype of NHL and the extent of the disease (stage) at the time point of first diagnosis.

Patients with NHL stage I (meaning with one single tumour) have a very good prognosis (with a 100 % probability of survival). Patients with stage II disease also have a favourable outcome. If the chest and/or abdomen are/is involved (stage III) or the *central nervous system* and/or *bone marrow* (stage IV), however, intensified therapy is required, which usually also results in good cure rates..

About 10-15 % of children and adolescents with NHL develop recurrent disease (relapse). Prognosis for these patients is generally unfavourable, even though for some of them (for example those with anaplastic large cell lymphoma or diffuse large cell B-cell lymphoma), outcomes are a bit better. The current *therapy optimising trial*s and future studies aim at improving the chances of cure for these patients, too.

Note: The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with childhood NHL. They do not predict individual

outcomes. NHL can show unpredictable courses, in both patients with favourable and patients with unfavourable preconditions.

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Glossary

acute lymphoblastic leukaemia	lymphoblastic leukaemia, predominant form of leukaemia in childhood and adolescence
allogeneic stem cell transplantation	transfer of stem cells from a donor to a recipient. The prerequisite for an allogeneic transplant is that the tissue characteristics of the donor and recipient are largely identical. The stem cells are obtained from the blood or bone marrow.
anaemia	„lack of blood“; reduction of the red blood pigment (haemoglobin) and/or the proportion of red blood cells (haematocrit) in the blood below the normal value typical for a given age. Signs of anaemia include palor, headache, dizziness, and fatigue.
anamnesis	medical interview, a patient’s history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
anthracyclines	substances derived from certain types of bacteria or artificially produced; used as cytostatics, they prevent cell division in various ways; they can also damage the cell membrane and cause the cell to die. Anthracyclines include, for example, daunorubicin, doxorubicin, epirubicin, idarubicin and mitoxantrone.
antigen	substance that appears foreign to the body; it stimulates the immune system to produce antibodies against it and can trigger an allergic reaction.
autologous stem cell transplantation	(re)transfer of blood stem cells, e.g. after a chemotherapy or radiotherapy; the patient receives his own cells that were previously taken from their own bone marrow or blood. Autologous stem cell transplantation may be an option, for example, for certain patients with lymphoma, neuroblastoma, soft tissue sarcoma, or a brain tumour.
B lymphocytes	subtype of lymphocytes; they develop in the bone marrow and are responsible for the recognition of pathogens and the formation of antibodies.
B-symptoms	certain non-specific symptoms that often occur simultaneously in cancer patients: recurrent fever (above 38°C) for no apparent reason, night sweats and unintentional weight loss (more than 10% of body weight in six months). The three symptoms are grouped together under the term B symptomatology. In this combination, they occur primarily in patients with Hodgkin

	lymphoma and Non-Hodgkin lymphoma and are associated with an unfavourable prognosis.
blood group	hereditary, usually stable, structural characteristics (blood group antigens) of blood components (e.g. AB0 blood groups) located on the cell walls of blood and other tissue cells;
blood stem cells	precursor cells of all blood cells, which give rise to red blood cells (erythrocytes), white blood cells (leukocytes), platelets (thrombocytes) and some other cells. This process is called blood formation. The various blood cells are formed in the bone marrow before they enter the blood stream.
blood transfusion	transfer of blood (whole blood) or blood components (e.g. red blood cells or platelets) from a donor to a recipient.
blood-brain barrier	barrier between the blood and the central nervous system (CNS) that is permeable only to certain endogenous and foreign substances, thereby enabling active control over the exchange of substances with the CNS;
bone marrow	site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone); in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells).
bone marrow puncture	removal of bone marrow tissue to examine the cells; during the puncture, a few milliliters of liquid bone marrow are drawn from the pelvic bone or sternum into a syringe with the help of a thin hollow needle. The puncture is performed under local anaesthesia in older children; a sedative may also be administered (sedation). For smaller children, a short period of anesthesia may be appropriate.
brain	the part of the central nervous system (CNS) located in the head; the brain is protected by the skull and the meninges and consists mainly of nerve tissue.
cancer predisposition syndrome	genetic disorders that can include malformations and intellectual disability in addition to an increased risk of tumors; according to current knowledge, about 10% of childhood and adolescent cancers develop due to a known hereditary change or cancer predisposition syndrome. Cancer predisposition syndromes include Louis Bar syndrome (= ataxia telangiectatica), Beckwith-Wiedemann syndrome, Down syndrome, Hippel-Lindau syndrome, Li-Fraumeni syndrome, MEN syndrome,

	neurofibromatosis and WAGR syndrome. The familial form of retinoblastoma is also part of it.
cell	the smallest functional unit in organisms with the ability to perform metabolism, involuntary muscle movement and reproduction and to respond to stimuli; each cell contains a nucleus and a cell body (cytoplasm) and is externally bounded by the cell membrane.
central nervous system	comprises the brain and spinal cord and is separated from the so-called peripheral nervous system; as a central organ of integration, coordination and regulation, it serves to process external sensory impressions as well as stimuli produced by the organism itself.
cerebrospinal fluid	fluid produced by cells of the cerebral ventricles; it floats around the brain and spinal cord to protect them from injury and provide them with nutrients.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
computed tomography	imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
cytoreductive	cyt-: part of the word meaning „cell“; reductive means „reducing“; decreasing the number of cells
cytostatics	drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or preventing them from multiplying. Cells that divide frequently are particularly affected.
echocardiography	ultrasound examination of the heart to check its performance (cardiac function); the position or structure of the heart valves and walls, the wall thickness of the heart muscle, the size of the heart and the ejected blood volume (pumping function of the heart) are examined and assessed, among other things.
electrocardiography	method of measuring the electrical activity of the heart
enzyme	substances, usually proteins, that initiate, accelerate and catalyze biochemical reactions in a desired direction; enzymes are responsible for the metabolism of all organisms. Almost all biochemical processes in the organism are controlled by enzymes (e.g. digestion, protein biosynthesis, cell division). In addition,

	they also play an important role in stimulus uptake and transmission as well as signal transduction within cells.
genetic	concerning the (level of) inheritance or genes; inherited
high-dose chemotherapy	the use of a particularly high dose of cell growth-inhibiting drugs (cytostatics); in the case of cancer, it aims to destroy all malignant cells. Since the haematopoietic system in the bone marrow is also destroyed, the patients own or foreign blood stem cells must then be transferred (autologous or allogeneic stem cell transplantation).
HIV	abbreviation for "human immunodeficiency virus"; HIV belongs to the retrovirus family. After an incubation period of varying lengths, usually several years, an infection leads to AIDS (acquired immunodeficiency syndrome), an immunodeficiency disease that is currently still incurable.
Hodgkin lymphoma	malignant disease of the lymphatic system; belongs to the malignant lymphomas and accounts for about 5% of malignant diseases in childhood and adolescence.
imaging	diagnostic procedures generating images of the inside of the body, such as ultrasound and X-ray examination, computed tomography, magnetic resonance imaging, and scintigraphy
immune system	the bodys own system for maintaining a healthy organism by defending against foreign substances and destroying abnormal body cells (e.g. cancer cells); the immune system has the ability to distinguish between self and foreign or dangerous and harmless; mainly the organs of the lymphatic system as well as cells distributed throughout the body (e.g. leukocytes) and molecules (e.g. immunoglobulins) are involved.
immunological	associated with the structure and function of the bodys own defense system (immune system); includes the recognition and defense mechanisms of an organism for foreign and endogenous substances and tissues.
infection	penetration of the smallest organisms (e.g. bacteria, viruses, fungi) into the body and subsequent multiplication within it. Depending on the characteristics of the microorganisms and the immune system of the infected person, various infectious diseases can occur after infections.
infusion	introduction of fluids into the body, usually over a long period of time and via a central venous catheter; an infusion is given, for

	example, to supply water, electrolytes, proteins and/or medication as part of intensive treatment.
injection	relatively rapid (as opposed to infusion) introduction of dissolved drugs into the body (for example, through the vein, into the muscle, under the skin);
intrathecal	“into or located within the cerebrospinal fluid canal / cerebrospinal fluid space”, which contains the cerebrospinal fluid (CSF)
intrathecal chemotherapy	administration of cell growth-inhibiting drugs (cytostatics) into the cerebrospinal fluid (CSF) canal, which contains the CSF
intravenous	means located within a vein or given into a vein; here: e.g. administration of a medication or fluid/suspension into the vein by an injection, infusion or transfusion.
lactate dehydrogenase	enzyme that plays a role as part of a metabolic process (lactic acid fermentation) in all cells and organs and is also detectable in the blood; an elevated LDH level in the blood can indicate cell damage in the body and (among other conditions) occur in many benign and malignant diseases or injuries.
leukaemia	malignant disease of the blood forming (haematopoietic) system and the most common cancer in children and adolescents (about 33%); depending on the origin of the malignant cells, a distinction is made between lymphoblastic and myeloid leukaemias. Depending on the course of the disease (fast or slow), a distinction is made between acute and chronic leukaemias.
Louis-Bar syndrome	hereditary disease; it is mainly characterized by degeneration of the central nervous system (CNS), an impairment of the immune system (immunodeficiency), dilated blood vessels of the eyes and skin (so-called telangiectasias) and an increased risk of cancer (so-called cancer predisposition syndrome). Degeneration of the CNS is associated with various neurological disorders, such as movement disorders (ataxia) and abnormal eye movements. The immunodeficiency often causes recurrent infections.
lumbar puncture	puncture of the spinal canal in the lumbar spine, e.g. to remove cerebrospinal fluid (CSF) or for the purpose of administering medication (so-called intrathecal treatment); in the case of cancer, a sample and examination of cerebrospinal fluid can be used to detect malignant cells; in the case of increased intracranial pressure due to a CNS tumour, cerebrospinal fluid removal (CSF) is also used to relieve pressure.

lymph nodes	small lenticular to bean-shaped organs that are part of the bodys immune system and are located in many parts of the body; they serve as filter stations for the tissue water (lymph) of a region of the body and contain cells of the immune system.
lymphatic system	collective term for lymphatic vessels, lymphatic vessel trunks, lymph nodes, lymphatic tissues (lymphocytes in connective tissue, mucous membranes, glands) and lymphatic organs (spleen, pharyngeal tonsils, bone marrow, thymus gland).
lymphocytes	subgroup of white blood cells that are responsible for the bodys own defenses, especially the defense against viruses; there are B and T lymphocytes. They are formed in the bone marrow, but partly only mature to full functionality in the lymphatic tissue (e.g. lymph nodes, spleen, thymus gland). They eventually enter the blood via the lymphatic vessels, where they take over their respective tasks.
lymphoma	collective term for lymph node enlargement of various causes
magnetic resonance imaging	diagnostic imaging method; very precise, radiation-free examination method for the visualization of structures inside the body; with the help of magnetic fields, cross-sectional images of the body are generated, which usually allow a very good assessment of the organs and many organ changes.
mediastinum	middle section of the thoracic cavity located between the two lungs
meninges	layers of connective tissue that protectively envelop the brain; the three meninges are joined to the outside by the skull bones. In the area of the spinal cord, the meninges merge into the three-layered spinal cord membrane, which surrounds the rest of the central nervous system.
molecular	at the level of molecules
monoclonal antibodies	antibodies produced by the derivatives of a single B lymphocyte (cell clone) that are completely identical; they can be genetically engineered for diagnostic and therapeutic purposes and target a small molecular segment (epitope) of a specific antigen.
oral	belonging to the mouth, through the mouth, from the mouth
outpatient	non-inpatient medical care: the patient does not stay overnight in the medical facility for diagnostic and/or treatment center, but can go home the same day.

petechiae	smallest, punctual bleedings of the skin and/or mucous membranes
physical examination	an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.
positron emission tomography	an imaging, nuclear medicine procedure based on the principle of scintigraphy, which can be used in cancer medicine to visualize tumours or metastases. To detect tumour tissue, a radioactively labeled sugar compound is administered. Since tumours have a higher metabolism than healthy tissue, the radioactive substance is increasingly taken up and stored by the tumour cells. The tumour cells enriched with this substance emit signals that are captured by a special camera (PET scanner) and converted into an image (tomogram).
prognosis	prediction of the course and outcome of a disease / prospect of recovery
prognostic factors	factors that allow an approximate assessment of the further course of the disease (i.e. the prognosis);
radiation therapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
radioactive radiation	radiation produced by the decay (nuclear decay) of radioactive substances; these are substances with unstable atomic nuclei that spontaneously transform by releasing energy. The energy released is emitted as ionizing radiation (high-energy particles and/or gamma radiation).
remission	temporary or permanent decrease or disappearance of the signs of cancer.
stem cell transplantation	transfer of haematopoietic stem cells after conditioning chemotherapy, radiation or immunosuppression of the recipient; the stem cells can be obtained either from the bone marrow or from the bloodstream. In the first case, the procedure of their transfer is called bone marrow transplantation, in the second case peripheral stem cell transplantation. Depending on the type of donor, a distinction is made between two forms of SCT: allogeneic SCT (stem cells from a foreign donor) and autologous SCT (own stem cells).
surgery	surgical intervention on or in the body of a patient for the purpose of treatment, less often also in the context of diagnostics;

	the surgical intervention is carried out with the help of special instruments, generally with the patient under anesthesia.
symptom	sign of illness
systemic	covering/includiing the entire body
T lymphocytes	subtype of lymphocytes (a form of white blood cells); they develop in the thymus gland and are responsible for the so-called cellular immune response; T lymphocytes play an important role in the direct defense against viral and fungal infections and control the activities of other immune cells (e.g. granulocytes).
therapy optimising trial	a controlled clinical trial (study) that aims to provide the best possible treatment for patients and at the same time to improve and develop treatment options; therapy optimisation is aimed not only at improving the chances of recovery, but also at limiting treatment-related side effects and long-term effects.
thymus gland	organ belonging to the lymphatic system below the thyroid gland; part of the bodys own defence system and significantly involved in the development of the immune system, especially during childhood; from puberty onwards, it loses its size and importance.
transplantation	transfer of tissues, organs or cells
tumour	groups of abnormal cells forming a growing lump, both benign and malignant
tumour lysis syndrome	metabolic changes due to tumour cell death as a consequence of cancer treatment, usually with large masses or cell counts, after chemotherapy; the changes are manifested by increased uric acid, potassium and phosphate levels, as well as a decrease in serum calcium concentrations, which can result in acute renal failure.
ultrasound	an imaging technique used to examine organs, in which ultrasound waves are sent through the skin into the body; at tissue and organ boundaries, the sound waves are reflected back, picked up by a receiver (transducer) and converted into corresponding images with the help of a computer.
WHO classification	international guideline developed by the World Health Organization (WHO) for classification, diagnosis and differentiation/grading of (malignant) diseases
Wiskott-Aldrich syndrome	congenital disease with coagulation disorder and immunodeficiency; typical features include skin bleeding, increased susceptibility to infections, eczema-like skin lesions and

	a tendency to allergic reactions as well as an increased risk of cancer. Wiskott-Aldrich syndrome is, therefore, also one of the cancer predisposition syndromes (CPS).
X-ray examination	imaging procedure that uses X-rays to visualize organs or parts of organs