Acute lymphoblastic leukaemia (ALL) - Brief Information

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Kinderkrebsinfo is sponsored by Deutsche Kinderkrebsstiftung
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1. General disease information

Acute lymphoblastic leukaemia (ALL) is a malignant cancer that arises within the haematopoietic system. ALL usually originates from the bone marrow, where the blood cells are produced. It is characterised by an overproduction of impaired white blood cells.

Healthy blood cells reproduce and regenerate at a normal, balanced rate. They undergo a complex maturation process. ALL interferes with this process:

The white blood cells (leukocytes) are unable to mature into functional cells and instead multiply rapidly and uncontrollably. This disturbs normal blood cell formation, so that healthy white blood cells, red blood cells (erythrocytes), and platelets (thrombocytes) can no longer be produced to the extent that is necessary.

Anaemia, infections, and bleeding tendencies can result and may be the first signs of acute leukemia. Since ALL is not limited to one specific region of the body, but can spread from the bone marrow into the blood and the lymphatic system, it can affect all organs and organ systems and is therefore – like all leukaemias – known as a malignant systemic disease.

ALL progresses rapidly. The spread of leukaemia cells and the resulting damage to other body parts can cause serious diseases, which – without the appropriate Treatment – are lethal within a few weeks or months.

2. Incidence

Comprising about 80% of childhood leukaemias, acute lymphoblastic leukaemia (ALL) is the most common form of leukaemia in children and adolescents, and it accounts for approximately one third of all cancers in this age group.

According to the German Childhood Cancer Registry, about 500 children and adolescents aged 0 to 14 years are newly diagnosed with ALL in Germany each year. Counting all patients up to 18 years of age, the incidence is about 550 to 600 new diagnoses per year. In general, ALL can occur at any age, including adults. The most commonly affected people, however, are children, with instances of ALL being the highest during the first five years of life. Boys are slightly more affected than girls.

3. Types of ALL

ALL is mainly characterised by a malignant transformation of immature precursor cells of lymphocytes. This transformation can occur during every stage of cell development (differentiation),
thereby affecting various subtypes of lymphocytes as well as their precursors. For this reason, there are various forms of ALL.

So-called B-ALL, for example, is based on progenitor cells of B-lymphocytes, while T-ALL forms from precursors of T-lymphocytes. A degeneracy in the early development stages is characterised by the prefix "pre". This results in the following ALL-subtypes:

- Pre-pre-B-ALL (now commonly referred to as pro-B-ALL)
- Common ALL
- Pre-B-ALL
- (mature) B-ALL
- Pro- and Pre-T-ALL
- Intermediate (cortical) T-ALL
- T-ALL

It is important to know that there are multiple forms of ALL, because when it comes to the course and prognosis of this disease, there are differences between each type to some extent. These differences are considered during the selection of a treatment plan.

4. Causes

The causes of acute lymphoblastic leukaemia (ALL) are largely unknown. It is known so far that the disease arises from the malignant transformation of precursor lymphocytes, and also, that this transformation can be 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, remains to be discovered.

For example, there is a known gene mutation in ALL that can be found in some newborns, even if they do not present with the disease until years later. Furthermore, not every child with this kind of genetic mutation will suffer from ALL. This suggests that, in addition to genetic factors, environmental influences can play a role in pathogenesis. It seems that many factors must come together for ALL to occur.

It is also known that children with certain inherited or acquired immunodeficiencies as well as young patients with chromosomal alterations (such as Down syndrome or Fanconi anaemia) have a higher risk of developing acute leukaemia than their healthy peers. Also, exposure to ionising irradiation and X-rays, certain chemicals and drugs as well as certain viruses have been reported to play a role in the development of leukaemia. However, for most patients no specific cause for the development of ALL can be identified.
5. Symptoms

The health problems (symptoms) caused by ALL usually develop within only a few weeks. They mainly occur due to the increase of malignant cells within the bone marrow as well as their spread into other organs and tissues. The uncontrolled production of leukaemia cells in the bone marrow increasingly suppresses the production of normal blood cells.

Children and adolescents suffering from ALL initially experience general symptoms such as fatigue, pain, and pallor. This is due to the lack of red blood cells (anaemia), the function of which it is to carry oxygen to cells throughout the body.

The lack of functional white blood cells (i.e. lymphocytes and granulocytes) prevents pathogens from being attacked and eliminated properly, thereby causing infections and fever. Another frequent symptom is bleeding, for example, under the skin (bruises, petechiae) or from mucous membranes such as the gums, owing to impaired blood coagulation as a result of low platelet counts.

The growth of leukaemia cells in the marrow of the long bones can cause bone and joint pain, especially in the limbs (arms and legs) and back. This pain can be so intense that the affected child may refuse to walk or run.

The malignant cells can also spread into the liver, spleen, and lymph nodes. Therefore, these organs may enlarge and subsequently cause problems, such as abdominal pain. In general, all organs can potentially be affected by ALL. If ALL spreads to the brain and its meninges, patients may suffer from headache, visual disturbances, nausea, vomiting, and other central nervous system impairments.

**Good to know:** The type and degree of symptoms of ALL vary individually. It is also important to know that the occurrence of one or more of these symptoms does not necessarily mean that they are caused by leukaemia. Many of these symptoms also occur in benign diseases that have nothing to do with leukaemia. However, if these symptoms occur or recur frequently or persist, a doctor should be consulted as soon as possible. If acute leukaemia is diagnosed, treatment must be started promptly.

6. Diagnosis

If the doctor, based on the young patient's history and physical examination, suspects acute leukaemia, he or she will first initiate a blood test. If the results promote the diagnosis of an acute leukaemia, a sample of the bone marrow (bone marrow biopsy) is required for confirmation.

For bone marrow tests and other diagnostic procedures, the doctor will refer the patient to a children's hospital with a paediatric oncology program (paediatric oncology unit).

6.1. Blood and bone marrow tests

Blood and bone marrow tests are needed to confirm the diagnosis of leukaemia as well as to determine the type. The tests include microscopic (cytomorphological), immunological, and genetic laboratory analysis of blood and bone marrow samples that distinguish ALL from other kinds of leukaemia (such as AML) and, furthermore, allow to define the specific subtype of ALL.
Knowing the subtype of ALL is necessary for appropriate therapy planning, because different forms of ALL have different biological characteristics and also vary regarding their response to treatment and, thus, prognosis.

6.2. Staging
Following the diagnosis of ALL and its subtype, it is important for treatment planning to know whether the leukaemia cells have spread to additional body compartments (other than the bone marrow), including the brain, liver, spleen, lymph nodes, testicles, or bones. Therefore, various imaging techniques, such as ultrasound, X-ray, magnetic resonance imaging (MRI), computed tomography (CT), and/or bone scintigraphy, may be used to evaluate spread of the disease.

To find out whether the central nervous system (brain and spinal cord) is affected, a sample of cerebrospinal fluid is taken and analysed for leukaemia cells (lumbar puncture).

6.3. Additional diagnostics before treatment begins
For treatment preparation, tests on the patient's cardiac function (electrocardiogram and echocardiography) and brain function (electroencephalography, evoked potentials) are performed.

Furthermore, additional bloodwork is needed to assess the patient's general health condition and to determine the patient's blood type (essential in case a blood transfusion may be necessary during the course of treatment). Also, the functions of certain organs (such as kidneys and liver) need to be evaluated by blood tests in order to rule out potential metabolic disorders that can have negative impact on the treatment.

Having collected all this information prior to treatment helps the doctors later to detect and thus treat treatment-induced changes earlier.

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. Therefore, you should always ask your doctor, based on the information above, which test your child needs and why.

7. Treatment
If acute lymphoblastic leukaemia (ALL) is being suspected or has been diagnosed, treatment should be started as soon as possible in a children's hospital with a paediatric oncology program. Only in such a treatment centre, highly experienced and qualified staff (doctors, nurses and many more) is guaranteed, since they are specialised and focus on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts.

The doctors (such as oncologists, radiologists, surgeons) in theses 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 and low rates of side effects.
7.1. Treatment methods

- **Chemotherapy** is the major backbone of ALL treatment. 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 leukaemia cells, a combination of cytostatics that function in different ways are usually given (polychemotherapy).

- **Radiation therapy** of the brain (cranial irradiation) is used for some patients in addition to chemotherapy to treat central nervous system involvement.

- **Stem cell transplantation:** For some patients, high-dose chemotherapy (and, partly, total body irradiation) followed by stem cell transplantation may be an option.

The goal of treatment is to eliminate the leukaemia cells in the body as extensively as possible, so that the bone marrow can resume its function as a blood cell-producing organ. In order to prevent or adequately manage the side effects of the intensive therapy, specific supportive care regimens have been established and now represent an important and efficient component of ALL treatment.

The intensity and duration of chemotherapy, the need for radiotherapy and/or stem cell transplantation, as well as the prognosis of the disease, depend on the subtype of ALL, on how extensively the leukaemia cells have spread throughout the body, whether the patient tolerates the treatment, and whether the leukaemia responds to it.

**Note for patients with mature B-ALL (B-AL):** This ALL subtype is not treated like the other forms of ALL. Patients with mature B-ALL will receive a treatment similar to that of mature B-cell Non-Hodgkin Lymphoma and are therefore not included in the following chapters.

7.2. Course of treatment

Treatment of children and teenagers with ALL consists of different steps. These steps (or phases) have different purposes. Therefore, they vary regarding their duration, treatment intensity, and drug combinations.

Each treatment period follows a different treatment plan (protocol), and each treatment plan is adapted to the patient's individual situation. The protocol the doctors decide to use for a patient depends, for example, on the subtype of ALL, the results of the staging, and other individual factors that are important for the patient's risk of recurrent disease. As a rule of thumb, the doctors will recommend more intense treatment if your child has a relatively high risk of relapse.

Usually, treatment will take about a total of two years, in particular if no stem cell transplantation is planned and/or the disease responds sufficiently to therapy. There will be both times spent as inpatient (about six months total with discharges in between) and outpatient (about one and a half years).

**The major elements of ALL treatment are:**

a. **Pretreatment** (cytoreductive preliminary phase) consists of a short, approximately one-week long, phase of chemotherapy using moderate dosages of one or two different agents. The
purpose of this phase is to reduce the often initially heavy burden of leukaemia cells gradually. This relatively gentle start helps the doctors to keep the metabolic products released by the dying leukaemia cells under control, which is important, because such metabolites can seriously harm the patient's organs, especially the kidneys (so-called tumor lysis syndrome).

b. **Induction therapy**: consists of an intense phase of chemotherapy using a combination of different agents. It aims at eliminating most of the leukaemia cells, thereby inducing remission in a short period of time. Induction therapy usually takes about five to eight weeks.

c. **Consolidation and intensification therapy**: takes several (about two to four) months and includes the use of various combinations of cytostatics. One major goal is to permanently eliminate the leukaemia cells that may be remaining from the induction phase and to maintain remission. Another major aim of this phase is to prevent the spread of ALL cells to the central nervous system (CNS). This is done by giving special cytostatics into the spinal fluid via a lumbar puncture (intrathecal chemotherapy). If the CNS is already affected by the ALL, cranial irradiation is recommended in addition to intrathecal chemotherapy.

d. **Reinduction therapy** consists of alternating courses of polychemotherapy, the intensity of which is comparable to that of induction therapy. Reinduction is to ensure complete destruction of leukaemia cells and thus minimise the risk of developing recurrent disease. Reinduction might take weeks to months, and intensive treatment courses alternate with chemotherapy pauses and discharge from the ward.

e. **Maintenance therapy**: This last phase of treatment is designed to eliminate all the leukaemia cells that may not be detectable but still have survived despite 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.

### 8. Therapy optimising trials

In Germany, diagnosis and treatment of almost all children and adolescents with acute lymphoblastic leukaemia (ALL) are performed according to the treatment plans (protocols) of "therapy optimising trials", so named because the treatment concepts of such trials are continuously being optimised based on the latest medical knowledge and the experience with former protocols. Therapy optimising trials are standardised and controlled studies that aim at steadily developing and improving treatment possibilities for cancer patients.

The trials are usually applied in numerous treatment centres, not only in Germany, but also abroad (multicentric and international studies). Currently, the following therapy optimising trials are available for children and adolescents with ALL in Germany. The patients with mature B-ALL (B-AL) are not considered here, since they receive a treatment for mature B-cell Non-Hodgkin’s lymphoma.

Please note that the first two studies listed below differ but slightly and are recruiting the same group of patients (patients with newly-diagnosed ALL, aged between 1 and 18 years). The choice
between the two is made by the local treatment team, depending on which of the two protocols the respective treatment centre is specialised in.

- **Trial AIEOP-BFM ALL 2009**: International multicentre therapy optimising trial for the treatment of children and adolescents aged 1 to 17 years with first diagnosis of ALL. The protocol is used by numerous treatment centres throughout Germany as well as in Austria, Switzerland, Italy, the Czech Republic, Israel and Australia. The German study center is located at the University Hospital Schleswig-Holstein, Campus Kiel (principal investigator: Prof. Dr. med. Martin Schrappe).

- **Trial COALL-08-09**: Multicentric therapy optimising trial of the GPOH for the treatment of children and adolescents aged between 1 and 17 years with newly diagnosed ALL, which was started on 01/10/2010. The study is performed by numerous paediatric oncology centres in Germany. The principal investigator is Prof. Dr. med. Martin Horstmann, University Hospital Hamburg-Eppendorf.

- **Trial Interfant-06**: International multicentric trial for infants in the first year of life with ALL or biphenotypic leukemia (subgroup of ALL). The German trial centre is located at the University Hospital Schleswig-Holstein, Campus Kiel, under the supervision of Prof. Dr. med. Martin Schrappe.

- **Register EsPhALL**: This register, which was opened in 2013, collects the data of patients with Philadelphiachromosome-positive ALL (aged between 1 and 17 years) who are treated as part of the BFM-, COALL- or Interfant trials. The register is sequel to the trial EsPhALL, which was completed at the end of 2012. Treatment recommendations remain as before. Study director for Germany and Switzerland is Prof. Dr. med. Martin Schrappe, University Hospital Schleswig-Holstein, Campus Kiel.

- **Trial ALL SCTped 2012 FORUM**: International, multicentric therapy optimising trial for patients (under 18 years of age) for whom allogeneic stem cell transplantation is an option. The trial was opened in 2013, its treatment protocols being applied by numerous paediatric oncology centers throughout Germany as well as in other European and some non-European countries. The international study coordinator is Prof. Dr. med. Christina Peters at the St. Anna Children’s Hospital in Vienna, Austria. The German trial centre is located at the Johann-Wolfgang-Goethe University Hospital, Frankfurt (study director: Prod. Dr. med. Peter Bader).

- **Trial IntReALL SR 2010**: International, multicentric therapy optimising trial for children and adolescents under 18 years of age who suffer a first, standard-risk relapse of ALL; the study centre is located at the Department of Paediatric Oncology and Haematology of the Charité Berlin (study director: PD Dr. Arend von Stackelberg).

- **Observation Trial ALL-REZ**: This trial collects data of recurrent disease patients (under 18 years of age) that are not included in above-mentioned study, such as children and adolescents with a second relapse or a first but high-risk relapse of ALL (principal investigator: PD Dr. Arend von Stackelberg, Department of Paediatric Oncology and Haematology of the Charité Berlin).
The major goal of therapy optimising trials is to continuously improve the treatment and, thus, the outcome of all ALL patients and to minimise treatment-related side effects. The experience with a previous trial will be incorporated into the subsequent protocol, thereby providing continuous optimisation and knowledge gain.

9. Prognosis

The chances of cure (prognosis) for children and adolescents with acute lymphoblastic leukaemia (ALL) have significantly improved due to the immense progress in diagnostics and treatment over the last four decades. Today’s modern diagnostic procedures and the use of intensive, standardised polychemotherapy protocols combined with optimised supportive care regimens result in current 10-year survival rates of about 90 %.

However, for children with unfavourable prognostic factors, such as high white blood cell counts at diagnosis, nonresponse to therapy, and/or certain hard-to-treat ALL-subtypes, survival rates are considerably lower than 90 %.

About 90 of the 550 to 600 children and adolescents (approximately one in seven patients) newly diagnosed with ALL in Germany per year develop recurrent disease.

Recurrent disease most frequently appears during the first two to three years after the initial diagnosis, while it is rather rare after five years following first diagnosis of ALL. The prognosis is generally worse than during the initial treatment, although in a subset of patients treatment success can still be achieved. The 5-year survival rates in children and adolescents with ALL relapse are currently at about 50 to 60 %.

Under the current therapy optimising trials and future studies, the chances of cure are continually improved for these patients.

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 ALL. They do not predict individual outcomes. Acute leukaemias can show unpredictable courses, in both patients with favourable and patients with unfavourable preconditions.
Bibliography


