SERVIER

Acute lymphoblastic leukaemia (ALL)

What is that?

Information for children and parents

Contents

Hi, I'm Teddy! I'll guide you kids through this brochure and explain it all to you. Come find me!

What is acute lymphoblastic leukaemia (ALL)?

Acute lymphoblastic leukaemia (ALL), also known as blood cancer, is a malignant disease of the blood producing organs. ALL arises from the bone marrow, the site of the body where the blood is made. The causes for its development are still only partially understood. Leukaemias are associated with an uncontrolled overproduction of immature, meaning not properly functioning white blood cells, which is known as malignant transformation of blood cells.

Healthy white blood cells (leukocytes) play an important role in the body's defense mechanisms against pathogens (immune defense). Their malignant transformation results in impaired immune defense.

Another problem is that the malignant cells (leukaemic blasts) proliferate fast. Therefore, they continuously choke off normal blood production. As a consequence, not enough healthy white blood cells, red blood cells (erythrocytes) and platelets (thrombocytes) are being made, thereby leading to infections, anemia and increased risk of bleeding as well as general fatigue. These conditions often are the first symptoms indicative of leukaemia.

ALL can spread from the bone marrow into the circulating blood, the lymphatic system (such as lymphatic vessels, lymph nodes, tonsils, spleen and thymus) as well as all other organ and organ systems. Therefore ALL is considered as a systemic disease

If not or inappropriately treated, the fast spread of leukaemic blasts will cause severe organ damage and lead to death within a few months.

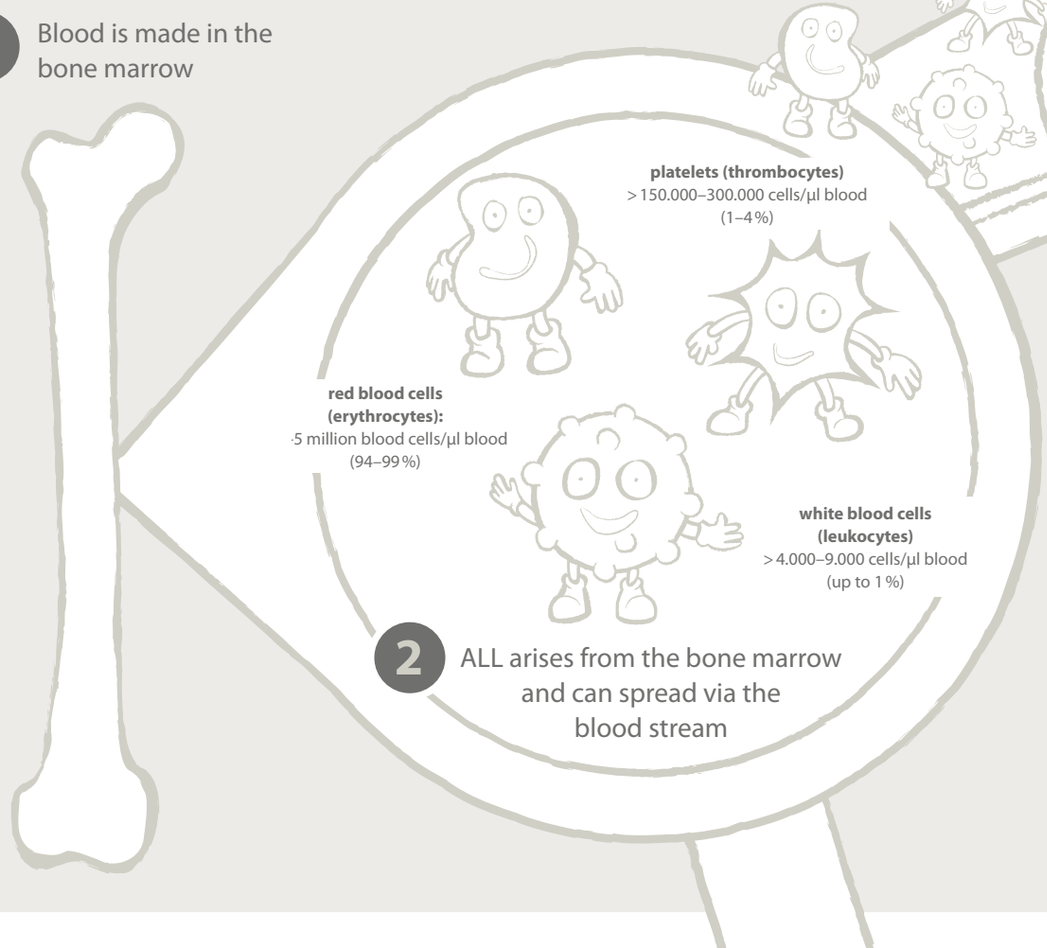
Incidence

Accounting for about 80% of all childhood leukaemias, ALL is the most frequent type of blood cancer in this age group. It constitutes about one third of all childhood cancers in children and adolescents. In Germany, about 500 children and teenagers are newly diagnosed with ALL per year (source: German Childhood Cancer Registry). Children between one and five years of age are most frequently affected.

Our blood is made in the bone marrow and consists of three important cell types: red blood cells, white blood cells and platelets. In patients with ALL, the bone marrow produces huge amounts of immature white blood cells, which do not function properly. Healthy white blood cells are an important part of the immune system. If they do not work properly the immune system will be very weak. As a consequence, it can't protect our body any longer and we become sick.

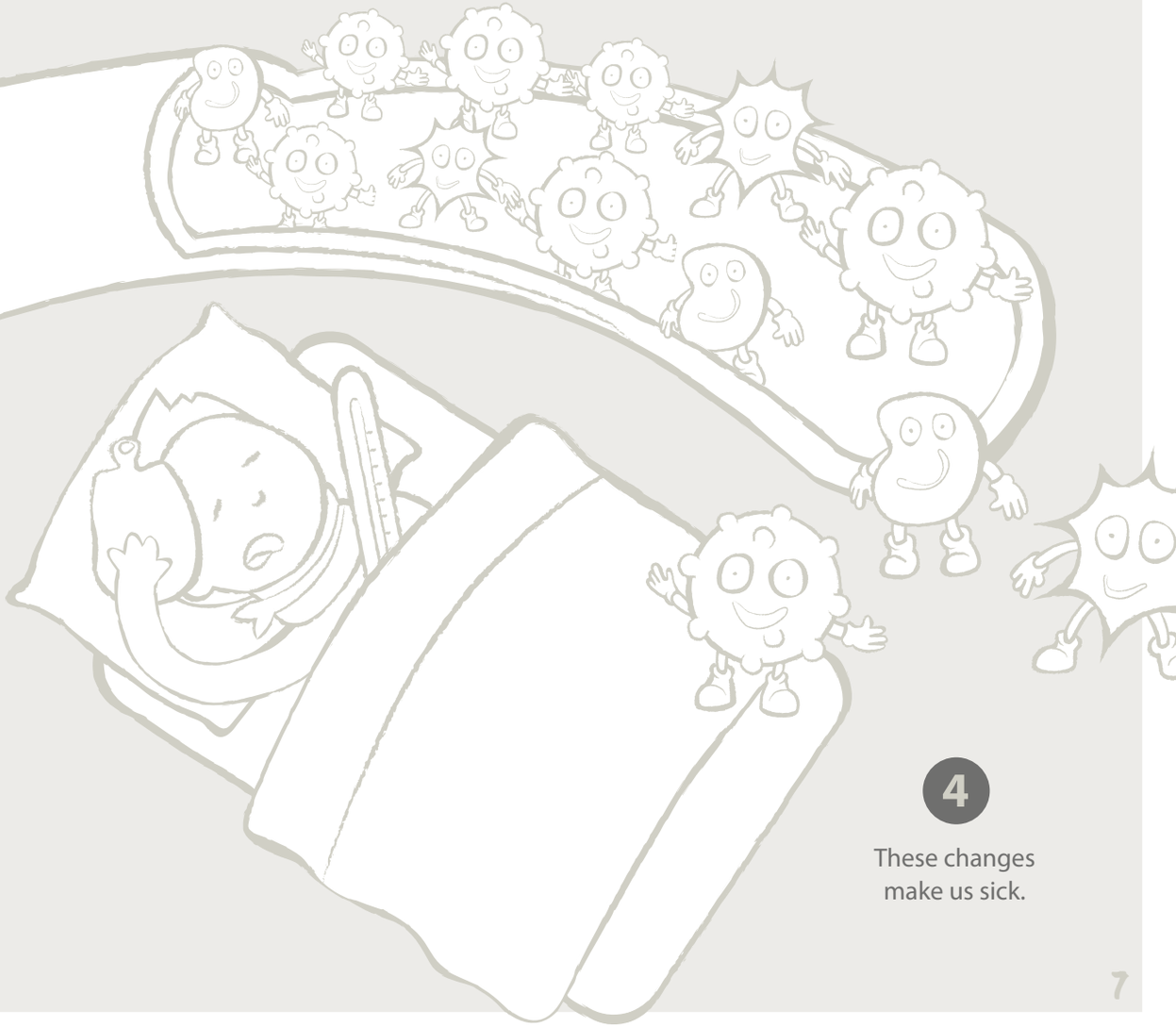
How does acute lymphoblastic leukemia (ALL) develop?

1 Blood is made in the bone marrow



2 ALL arises from the bone marrow and can spread via the blood stream

3 In patients with ALL, the white blood cells are sick and can't work properly. Also, many more white blood cells are made than in a healthy person. They take the space away from the healthy blood cells and platelets.



4 These changes make us sick.

ALL Subgroups

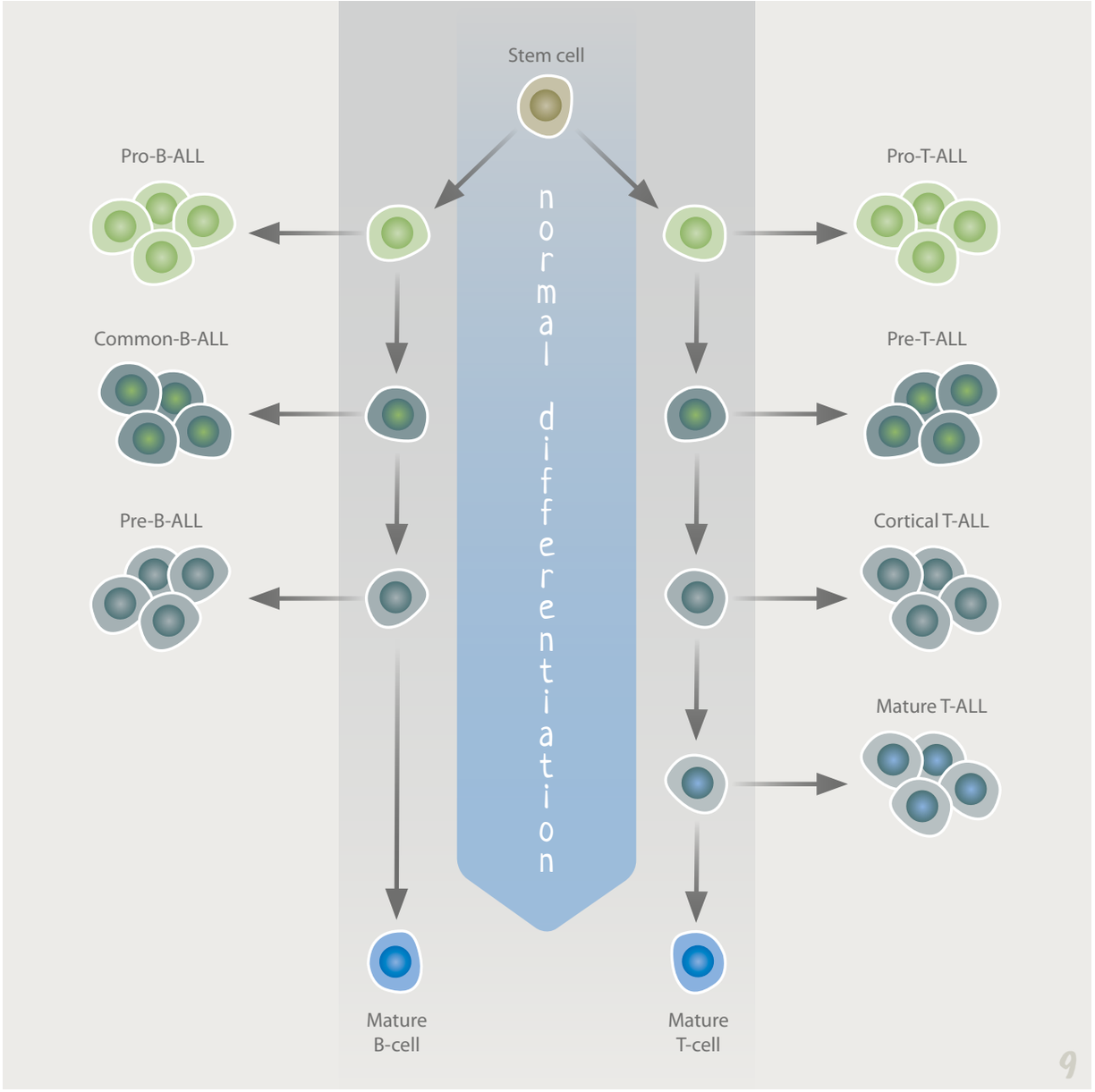
ALL arises from the malignant transformation of immature precursor cells of lymphocytes. These are a subgroup of white blood cells that are responsible for the body's immune defense, in particular for fighting viruses.

There are two types of lymphocytes: B- and T-cells. B-ALL develops from B-precursor and T-ALL from T-precursor cells. The prefixes "pre-" and "pro" indicate that malignant transformation started at a certain, early developmental stage.

Hence, the following ALL-subgroups are differentiated:

- pre-pre-B-ALL (today also named pro-B-ALL)
- common ALL
- pre-B-ALL
- pro-T-ALL
- pre-T-ALL
- intermediate (cortical) T-ALL
- mature T-ALL

The reason for this division into different subtypes is that these often are associated with different courses of the disease and probabilities of survival (prognosis). These differences are considered during treatment planning.



Causes

The causes for the development of ALL are mostly unknown. However, it is known that children with certain hereditary chromosome alterations (for example Down-Syndrome or Fanconi-Anemia) or with acquired immune defects have a markedly higher risk to develop leukaemia. Also ionizing radiation and x-rays, certain chemical substances and drugs can play a role.

Symptoms

Symptoms of ALL are caused by the growing mass of malignant cells in the bone marrow, other organs and tissue as well as by the impaired production of healthy blood cells: fever of unknown origin, persistent nose bleeds, frequent bruising and bleeding gums, headaches and fatigue are direct consequences of anemia and often the first symptoms of ALL. About a fifth of patients suffer from nocturnal bone and joint pain that is independent of activity. Abdominal pain and painless testicular swelling as a result of involvement of abdominal and reproductive organs are less frequent.

The causes for ALL are still a mystery, however, it is known that this disease can be inherited. The impaired production of healthy blood cells can cause nose and gum bleeds, pallor, bruises, headaches and fatigue.

Diagnosis

If the doctor considers a patient's history and physical exam findings indicative of leukaemia, a blood test is recommended.

If the results of the blood test support the suspected diagnosis of leukaemia by showing certain characteristics, a bone marrow sample (taken by bone marrow puncture and/or biopsy) is required to confirm it and the child will be admitted to a hospital with a pediatric hematology/oncology program.

If the diagnosis of acute leukaemia is confirmed in the hospital, more tests will be done. These help to find out, whether it is ALL versus another form of acute leukaemia, the acute myeloid leukaemia (AML) and to determine the ALL subtype as well as the patient's individual risk factors. These special tests include cytomorphological[b], immunological[c] and genetic[d] analyses.

Further investigations serve to assess the spread of the disease, such as brain, liver, spleen, lymph node or bone involvement. These tests include diagnosting imaging such as ultrasound and x-rays, magnet resonance imaging[e] (MRI) and computed tomography[f] (CT). Also, a lumbar puncture is required to obtain cerebrovascular fluid (CSF) samples to be checked for leukaemic blasts.

Prior to the start of therapy, additional tests are usually done.

Treatment planning – Choice of treatment strategy and risk stratification

After the diagnosis has been confirmed, treatment needs to be planned based on so-called risk-factors, which have been shown to impact the patient's prognosis.

These risk-factors include, in addition to the type of ALL subgroup, the presence or absence of specific genetic characteristics of leukaemia cells and the response of the disease to therapy. This response is defined by the reduction of leukaemic blasts in blood and bone marrow at certain time points of therapy. In order to assess the treatment response, blood and bone marrow samples are obtained from the patient at those time points and analyzed under the microscope. In addition, samples are investigated by highly sensitive molecular (submicroscopic) techniques, which help to detect remaining leukaemic blasts after cessation of treatment. These techniques are capable of detecting remaining blasts, even when the microscope does not reveal anything (monitoring of minimal residual disease, MRD).

By knowing the patient's individual risk factors associated with the disease, the caregiver team gets a better idea of how the leukaemia may respond to particular treatment approach and how high the risk of developing recurrent disease is. Currently, three risk groups have been defined for ALL: patients with low, intermediate and high risk for non-response to treatment and recurrent disease.

This stratification makes individual treatment planning possible, and therefore is of crucial relevance for a patient's chance of survival.

Treatment

ALL treatment consists of intensive chemotherapy. By using different agents that inhibit cell proliferation (cytostatic agents), the goal is to eliminate 99 % of leukaemic blasts within the first four weeks of therapy. To protect the central nervous system from potential involvement, patients also receive chemotherapy given directly into their CSF and maybe, at a later time point, also radiotherapy to the brain (cranial radiotherapy). During the intensive phase of therapy, patients are treated as inpatients, while the milder maintenance therapy is usually given to outpatients. Treatment time for ALL is generally two years.

Chemotherapy means treatment with agents that inhibit cell growth (cytostatic agents). Chemotherapy aims at destroying all leukaemic blasts, thereby enabling the bone marrow to resume its function as a blood producing organ. Patients with an increased risk of developing recurrent disease also receive cranial radiotherapy to in order to also eliminate leukaemic blasts that may have spread to the brain. In some rare circumstances, some patients with primary ALL may also need stem cell transplantation.

At the beginning, ALL is treated at the hospital, where you will receive special medication. Once you're back home, you can take most of your meds as pills or liquids.

Chemotherapeutic treatment of ALL patients generally consists of several phases with different durations, intensities and combinations of cytostatic agents.

The choice of treatment plan for each patient depends on the individual risk group. The higher the risk of recurrent disease, the more intensive the treatment will be.

If no stem cell transplant is required, or the patient does not develop recurrent disease, the total treatment time is two years. Taken together, it consists of multiple inpatient stays for the intensive therapy elements (about half a year) and a rather mild, mostly outpatient treatment phase (about one and a half years).

Relevant treatment elements are:

a. Prephase-therapy (cytoreductive prephase):

this element consists of a brief chemotherapy (one week) with the agents prednisone and methotrexate, the lateris given directly into the cerebrovascular fluid (intrathecally[9]). The pre phase serves as the introduction to therapy and aims at reducing the initially large number of leukaemic blasts in a stepwise approach, thereby protecting the body from an overload of dead cells.

b. Induction/consolidation therapy:

this phase takes eight weeks and includes intensive chemotherapy with several anticancer agents, such as prednisone (PRED) or dexamethasone (DEXA), vincristine (VCR), daunorubicin (DNR), asparaginase (ASP) and methotrexate (MTX), followed by cyclophosphamide (CPM), cytarabine (ARA-C) and 6-mercaptopurine (MP) after the first four weeks.

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The goal is to eliminate most of the leukaemic blasts in a short period of time, which means to achieve remission. In remission, a patient's blast count in the bone marrow is less than 5 %.

c. Extracompartmental therapy:

the important part of this phase is the preventive (prophylactic) treatment of the central nervous system. This is done by giving certain anticancer agents (methotrexate) both directly into the spinal canal (intrathecal chemotherapy) and intravenously. Some patients, for example those with known central nervous system involvement of leukaemia, also receive radiotherapy of the brain. These treatments help to prevent leukaemic blasts from spreading to the central nervous system or further proliferate there, respectively.

d. Reinduction therapy:

the intensity of this treatment element is similar to induction therapy and also consists of similar combinations of cytostatic agents given in high doses. The aim is to completely eliminate as many more leukaemic blasts as possible, thereby minimizing the risk of recurrent disease. The reinduction phase usually takes six weeks.

e. Maintenance therapy:

this last, long phase of therapy aims at destroying all those blasts that are remaining despite of the preceeding intensive elements. Maintenance therapy consists of a milder chemotherapy regimen with 6-mercaptopurine (MP) or thioguanine (TG) plus methotrexate (MTX). Patients are mostly treated as outpatients during this phase, which means that they can even attend kindergarten or school, if their overall condition allows so. Maintenance therapy lasts as long as a total treatment time of two years is completed.

Prognosis

Due to the enormous advances in treatment strategies, the chances of cure (prognosis) for children and adolescents with ALL have largely improved over the last four decades.

With today's modern diagnostic tools and intensive, standardized combination chemotherapy regimens, about 90 % of patients survive (10-year-survival rate).[1]

The prognosis of an individual patient mainly depends on the personal risk factors and the response of the disease to therapy.

Despite of the intensive treatments, the survival rates for patients with unfavorable risk factors (such as bad response to treatment, unfavorable genetics) are far below 90 %. Currently ongoing treatment optimization studies serve to find strategies for improving survival for these patients as well.[2,3,4]

During the last phase of treatment, you will be outpatient. That means, that you'll be back at home and can attend kindergarten or school again. You only have to go to the hospital for regular check-ups.

Glossary

[a] **antibody**
Proteins of the globulin-group, that are produced by the body's immune system as a protective response to foreign bodies or pathogens (antigens), respectively. Antibodies specifically bind to these antigens, thereby leading to different ways of eliminating them. Antibodies are made by a certain type group of white blood cells, the B-lymphocytes, also known as plasma cells.

[a] **cytomorphological**
refers to shape and structure of cells (under the microspcope); cytomorphology is the science of the celle shape and structure *Examples Pediatric Oncology/Hematology:* cytomorphologicalassessment of bone marrow and blood samples is part of the diagnostic routine when a hematological disease, such as a leukemia, is suspected.

[c] **immunological**
refers to the structure and function of the body's immune system; consists of an organism's recognition and protection mechanisms for the body's own as well as foreign tissues and pathogens.

[d] **genetic**
refers to hereditary factors or genes, respectively.

[e] **magnetic resonance tomography/ -imaging** (MR/MRI)
diagnostic imaging procedure; very precise, radiation-free technique for imaging certain inner structures (soft tissues) of the body; specifically arranged magnetic fields produce tomographic pictures which allow a very detailed assessment of the inner organs.

[f] **computed tomography** (CT)
diagnostic imaging procedure using multiple x-rays to create tomographic images of body regions of interest.

[g] **intrathecal** (i.th.)
„into the spinal canal", that contains the cerebrovascular fluid (CSF)

Literatur

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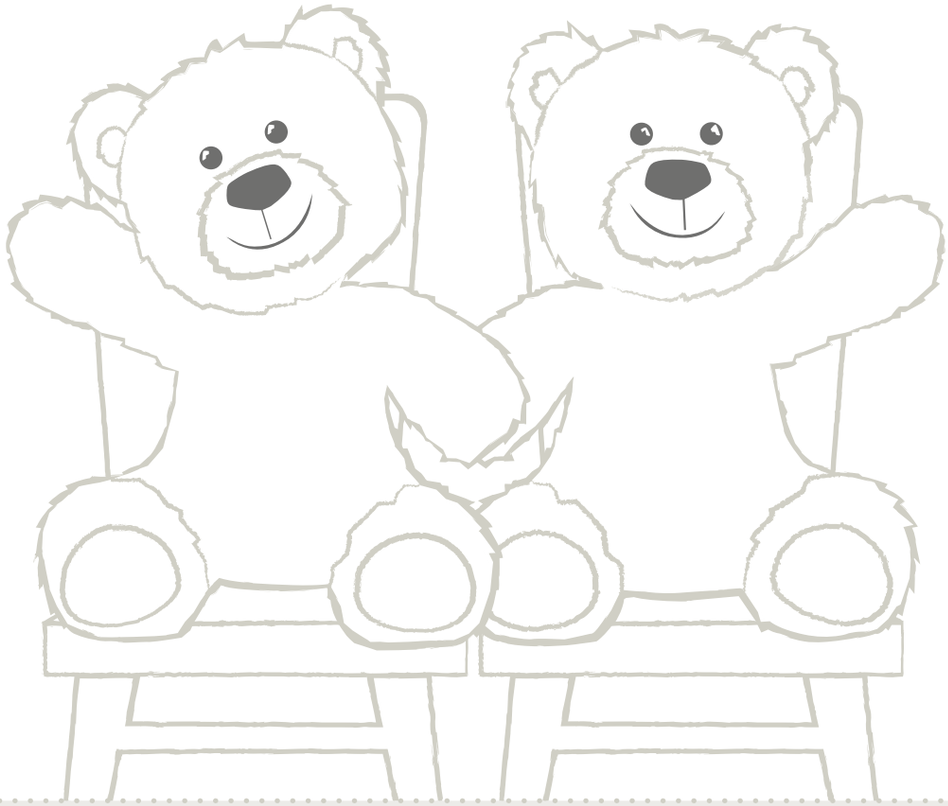
Leitlinie Akute lymphoblastische Leukämie – ALL – im Kindesalter
http://www.awmf.org/leitlinien/detail/ll/025-014.html

My teddy-bear **family** in the waiting room



Links

Information on ALL:

- https://www.kinderkrebsinfo.de/diseases/leukaemias/pohpatinfoall120060414/pohpatinfoallkurz/index_eng.html

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