Acute lymphoblastic leukemia

This article has been translated from WikiSkripta; the **formatting** needs to be checked.

Template:Infobox - nádor

Acute lymphoblastic leukemia (ALL) is a disease of the group of **malignant lymphoproliferative** disorders arising from the transformation of a hematopoetic stem cell of a lymphoid lineage. These cells lose their ability to differentiate, but retain their ability to proliferate beyond physiological regulation. It is the **most common malignancy of childhood** with an incidence of 7.7 / 100,000 in the age group 1–5 years, in adolescence the incidence decreases with another gradual increase in senior age. In total, in the age group over 18 years, the annual incidence in the Czech Republic is 1 / 100,000 inhabitants. The incidence is higher in patients with Down syndrome.

A related disease is **lymphoblastic lymphoma** (LBL), whose cells morphologically and immunophenotypically correspond to ALL cells. It often affects the mediastinum and is usually based on the T-line. The difference compared to ALL is in no or only minimal bone marrow infiltration and the absence of peripheral blood blasts. It is also a very aggressive malignancy, similar treatment regimens are used as in ALL.

Both of these diseases, ALL and LBL, can be **derived from B or T cell precursors** , with about 3/4 of the cases being B-line.

Classification

náhled|180px|vpravo| Acute lymphoblastic leukemia (type L1) in a three-year-old boy. There are slight differences in the size and density of chromatin, the minimum cytoplasm. Some cells have a nucleolus.The classification according to the EGIL group (European Group for the Immunological Characterization of Leukemia) is based on the immunophenotype of malignant cells determined by flow cytometry and roughly corresponds to the degree of maturity of lymphoblasts:

- **B-line:** (CD19+ and/or CD79a+ and/or CD22+)
  - **pro-B ALL:** TdT+, CD10+
  - **common-B ALL:** TdT+, CD10+, cIg– (most common)
  - **pre-B ALL:** TdT+, CD10+, cytoplasmatic cIg+, surface Ig–
- **T-line:** (CD3+ and CD7+)
  - **pro-T ALL:** TdT+, CD2–, CD5–, CD8–, CD1a–
  - **pre-T ALL:** TdT+, CD+ and/or CD5+
  - **thymic-T ALL:** TdT+, CD1a+
  - **mature-T ALL:** TdT+/–, CD1a–, mCD3+, TCRαβ+ or TCRγδ+

The 2016 revision of the **WHO classification** divides ALL into:

- B-lymphoblastic leukemia/lymphoma
  - B-lymphoblastic leukemia/lymphoma, not otherwise specified
  - B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- T-lymphoblastic leukemia/lymphoma

The most common recurrent genetic aberrations present in ALL are:

- ***BCR-ABL1*** – A fusion gene occurring pathognomically in chronic myeloid leukemia (CML), the so-called Ph - chromosome (Philadelphia) caused by t (9; 22) translocation. It is present in about 20% of ALL cases, more in senior age. Previously, it was a Ph- positive ALL group with the worst prognosis, now significantly improved by the inclusion of tyrosine kinase inhibitors in standard chemotherapeutic treatment.
- ***KMT2A-AF4*** – Fused gene caused by trasnlocation at t(4;11), worse prognosis of the disease.
- ***ETV6-RUNX1*** – Fusion gene mainly in childhood, better prognosis and treatment response.
- **Hyperdiploidie** (47-65 chromossomes) – Indicates a better prognosis in childhood.
- **Hypodiploidie** (less than 46 chromossomes) – Indicates a worse prognosis in children.
- ***Ph*-like ALL** – These are ALL with a heterogeneous group of genetic aberrations (especially CRLF2 gene fusion, genedisorders in JAK / STAT and ABL signaling pathways, deletion in IKZF1 gene), which despite the absence of BCR-ABL1 fusion genehave a similar gene profile expression as Ph- positive ALL and unfavorable prognosis.

Causes

The change from one of the cells to a tumor cell is usually due to chromosomal disorders or mutations in its genetic information . These disorders cause the cell to divide uncontrollably and cease to respond to the regulatory action of the organism. The reason for the mutation is not always known exactly. This may be due to exposure to certain

factors such as **chemicals and radioactive radiation** . Undoubtedly, the presence of an **inherited genetic predisposition to oncological diseases** is also important . However, the greatest influence will be a simple coincidence and the escape of a malignant cell from the body's immune surveillance.

Symptoms

The symptoms are very non-specific at first and may resemble other diseases. Common are the so-called **B-symptoms** , which include **weight loss** of at least 10% in 6 months, **sub- to febrile fever** of non-infectious origin and night or day heavy **sweating** . In addition, **symptoms of anemia** (fatigue, inefficiency, dyspnoea, in extreme cases myocardial infarction or brain hypoxia), **infections** due to leukocytopenia (most often respiratory, unresponsive to conventional ATB treatment) and **bleeding** due to thrombocytopenia (petechiae, epistaxis, or even more severe bleeding). **Bone pain** is a common and relatively typical symptom of ALL . Variousneurological symptoms may be associated with CNS infiltration. In about half of the cases, **lymphadenopathy** is present in various locations, sometimes **hepatomegaly** or **splenomegaly** .

upright=1.4|náhled|video in english: definitions, symptoms and complications, diagnosis, treatment

Diagnosis

There is regular anemia a thrombocytopenia of various degrees in the blood picture, the number of leukocytes may be increased, decreased, but also normal. Young bone marrow precusor cells - **blasts** - are present in the differencial leukocyte count.

In biochemical examination, elevation of lactate dehydrogenase (LD), C-reactive protein (CRP), there may be signs of spontaneous tumorysis syndrome (renal insufficiency, hyperkalemia, hyperphosphatemia, hyperuricemia). Coagulopathy with prolonged PT and aPTT coagulation times , hypofibrinogenemia, and D-dimer elevation is also common in ALL .

The basic diagnostic method is a microscopic examination of a peripheral blood smear and especially a bone marrow aspirate taken from a **sternal puncture or trepanobiopsy** - the so-called myelogram . In the marrow we find infiltration of populations of PAS (periodic acid - Schiff) positive and MPOX (myeloperoxidase) negative blasts. A key test in the diagnosis of acute leukemias is flow cytometry of the bone marrow or peripheral blood, which distinguishes ALL, AML and other rare types of acute leukemias.

Any patient with a finding of gross pathology in the blood picture and / or the presence of blasts should be referred immediately for further diagnosis at a specialized hematooncology center!

In the case of lymphoblastic lymphoma without bone marrow infiltration, **histology and immunuhistochemistry** of the pathological node resection are performed and the extent of the involvement (staging) is determined using **CT of the chest and abdomen.**

Lumbar puncture is also performed with cytological and flow cytometric examination of the cerebrospinal fluid due to the risk of CNS infiltration by this disease.

Other now standard laboratory tests necessary for proper risk stratification and treatment management are cytogenetic examination of karyotype and chromosomal aberrations using FISH (fluorescence in-situ hybridization) and more detailed analysis of fusion genes and other genetic aberrations by **molecular genetic methods** (PCR or next-generation sequencing).). PCR and flow cytometry are also used to detect so-called minimal residual disease (MRD) during and after treatment, when blasts may remain in the marrow below the limit of detection by microscopic methods.

Treatment

ALL treatment takes place in specialized hematooncology centers for patients of childhood or adulthood. Combination regimens consisting of chemotherapy, immunotherapy, tyrosine kinase inhibitors, corticoids, radiotherapy, and hematopoietic stem cell transplantation are used.

- **Intensive treament** of younger patients (up to 55 years) consists of several steps:

1. **Induction** - The most intensive part of treatment aimed at inducing complete remission , ie. destroy the entire tumor population detectable by microscopic examination in a myelogram. Ideally, even minimal residual disease can be eradicated at the level of detection by flow cytometry or molecular genetic methods. This phase of treatment lasts about 2 months and in adults it is given during hospitalization (in contrast, in children almost all treatment takes place on an outpatient basis). In patients with CNS infiltration or large mediastinal lymphadenopathy, **radiotherapy** of the affected area is also performed
2. **Consolidation** – A phase of treatment to maintain complete remission and further eliminate minimal residual disease.
    1. **Lower risk** patients – Several cycles of treatment lasting about 12 months, in adults in a combined outpatient and inpatient regimen, in children on an outpatient basis.
    2. **Higher risk** patients – These are patients with BCR-ABL1 , KMT2A-AF4 , baseline hyperleukocytosis , immunophenotype pro-B, pro-T, pre-T and mature-T, or persistent minimal residual disease after induction. After 1-2 cycles of consolidation chemotherapy, allogeneic hematopoietic stem cell transplantation is performed (see below).
3. **Maintenance treatment** – Outpatient treatment to reduce the risk of late relapses lasts about 2 years. It is

usually not given after allogeneic transplantation.

- **Paliative and symptomatic treatment** – For elderly patients unable to undergo more intensive, more toxic curative treatment and for recurrently relapsing diseases where other treatment options have been exhausted.

- **Treatment of relapse of primary refractory disease:**
  - Rescue chemotherapeutic regimens - They have high toxicity and low effectiveness, in the conditions of the Czech Republic they are now displaced by more modern treatment modalities.
  - Monoclonal antibodies to B-ALL - **Blinatumomab** (bispecific anti-CD19 / anti-CD3 antibody) and inotuzumab ozogamicin (anti-CD22 immunoconjugate and calicheamycin cytostatics).
  - The purine analog **nelarabine** in T-ALL.
  - 2nd and 3rd generation **tyrosine kinase** inhibitors **dasatinib and ponatinib** in relapsed Ph- positive ALL.
  - **CAR-T lymphocytes** - Genetically modified T-lymphocytes of a patient with an inserted gene for a chimeric antigen receptor (CAR) directed against one of the antigens on the surface of blasts, most often CD19. Highly effective and expensive treatment with specific toxicity (cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome). In the Czech Republic, B-ALL is currently covered by public health insurance only for patients under 25 years of age.
  - Treatment with new drugs in **clinical trials**.
  - Curative treatment of relapse must always be followed by a**llogeneic hematopoietic stem cell transplantation** after induction of the 2nd complete remission , otherwise the chance of maintaining long-term remission is essentially zero. In elderly patients unable to undergo allogeneic transplantation, treatment of relapse is always palliative.

- **Allogeneic hematopoietic stem cell transplantation** - The source of cells today is almost always peripheral stem cells washed into the peripheral blood by mobilization of G-CSF (granulocyte colony stimulating factor). Stem cells removed by puncture directly from the bone marrow are now used only exceptionally in specific indications. Before the transplant itself, the patient is given a so-called **preparatory regimen** - a combination of cytostatics and immunosuppressants, sometimes with whole-body irradiation. The preparation regimen can be **myeloablative** (in younger patients) or **reduced intensity / non-myeloablative**, for elderly patients). The stem cell donor can be an HLA-matched sibling, an HLA-matched unrelated donor from the registry, or an alternative mismatched donor (an unrelated donor with a partial match or a haploidentical donor from the patient's family). The age of feasibility of allogeneic transplantation is approximately 65-75 years of age, but each patient is assessed individually on the basis of biological age, comorbidities, previous treatment complications and the availability of a suitable donor.
- **Autologous hematopoietic stem cell transplantation** - It is no longer routinely used in ALL today, it is rather a backup option for patients who do not have a suitable donor, or for elderly patients.

Prognosis

The prognosis of ALL is highly variable and depends on many factors, especially age and risk stratification. With current treatment, complete remission in children can be achieved in more than 95% and long-term survival in almost 90%. In adults, the situation is less favorable. In patients under 55 years of age, complete remission is induced depending on the risk stratification in 80-90%, but due to frequent relapses, only 50-60% of these patients achieve long-term survival. In elderly patients treated intensively, long-term survival is between 20-40%, patients treated palliatively have a poor prognosis with a median survival of weeks to several months.

References

Related articles

- Leukemia
- Acute myeloid leukemia
- acute promyelocytic leukemia
- Chronic myeloid leukemia
- Chronic lymphocytic leukemia
- Hairy cell leukemia

References

- BÜCHLER, Tomáš. *Speciální onkologie*. 2. vydání. Praha: Maxdorf, [2020]. Jessenius. ISBN 978-80-7345-651-1.
- MAYER, Jiří, et al. Léčebné postupy v hematologii : doporučení České hematologické společnosti České lékařské společnosti Jana Evangelisty Purkyně. 1. vydání. 2016. ISBN 978-80-260-9718-1.
- Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J*. 2017;7(6):e577. Published 2017 Jun 30. doi:10.1038/bcj.2017.53. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520400/
- Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. doi: 10.1182/blood-2016-03-643544. Epub 2016 Apr 11. PMID: 27069254. https://pubmed.ncbi.nlm.nih.gov/27069254/
- Mohseni M, Uludag H, Brandwein JM. Advances in biology of acute lymphoblastic leukemia (ALL) and therapeutic implications. *Am J Blood Res*. 2018;8(4):29-56. Published 2018 Dec 10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6334189/

Template:Navbox - onemocnění krve