Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is a disease from the group of **malignant lymphoproliferations** arising from the transformation of the hematopoietic stem cell of the lymphoid line. These cells lose the ability to differentiate, but retain the 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 of 1–5 years, in adolescence the incidence decreases with a further gradual increase in senior age. Overall, in the age group over 18 years, the annual incidence in the Czech Republic is 1/100,000 of the population. The incidence is higher in patients with Down syndrome..

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

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

Classification

náhled|180px|vpravo|Akutní lymfoblastická leukemie (typ L1) u tříletého chlapce. Jsou patrné mírné rozdíly ve velikosti a denzitě chromatinu, minimum cytoplazmy. Některé buňky mají jadérko.Classification according to **egil** *(European Group for the Immunological Characterization of Leukemia)* is based on **the immunophenotype** of malignant cells detected by flow cytometry and roughly corresponds to the degree of maturity of lymphoblasts:

- **B-lines:** (CD19+ and/or CD79a+ and/or CD22+)
  - **pro-B ALL**: CD10+
  - **common-B ALL:** CD10+, cIg– (most common)
  - **pre-B ALL:** CD10+, cytoplasmic cIg+, superficial Ig–
- **T-line:** (CD3+)
  - **pro-T ALL:** CD7+, CD2–, CD5–, CD8–, CD1a–
  - **pre-T ALL:** CD2+ and/or CD5+ and/or CD8+
  - **thymic-T ALL:** CD1a+

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*** – Fusion gene occurring pathognomically in chronic myeloid leukemia (CML), the so-called **Ph-chromosome** (Philadelphia) caused by translocation t(9;22). It is present in about 20% of ALL cases, more in the elderly. Previously, *the Ph-positive* ALL group was the worst prognosis, now significantly improved by the inclusion of tyrosine kinase inhibitors in standard chemotherapy treatment.
- ***KMT2A-AFF1*** – Fusion gene caused by translocation t(4,11), worse prognosis of disease.
- ***ETV6-RUNX1*** – Fusion gene present mainly in childhood, better prognosis and response to treatment.
- **Hyperdiploidy** (47-65 chromosomes) – In childhood, it indicates a better prognosis.
- **Hypodiploidy** (less than 46 chromosomes) – In childhood, it indicates a worse prognosis.
- ***Ph*-like ALL** – This is an ALL with a heterogeneous group of genetic aberrations (mainly *CRLF2* gene fusion, gene disorders in the JAK/STAT and ABL signaling pathways, deletion in *the IKZF1* gene), which, despite the absence of the *BCR-ABL1* fusion gene, have a similar gene expression profile as *Ph-positive* ALL and an unfavorable prognosis.

Causes

The change of one of the cells to a tumor cell is usually the result of chromosomal disorders or **mutations in its genetic information**. These disorders cause the cell to begin to divide uncontrollably and cease to respond to the regulatory action of the organism. The reason for the mutation is not always exactly known. It can be exposure to some provoking 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 escape of a malignantly altered cell to the immune surveillance of the organism.

Speeches

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** of non-infectious origin and night or even daytime severe **sweating**. There are also **symptoms of anemia** (fatigue, inefficiency, shortness of breath, in extreme cases to myocardial infarction or brain hypoxia), **infection** as a result of leukocytopenia (most often respiratory, unresponsive to conventional ATB treatment) and b**leeding manifestations** due to thrombocytopenia (petechiae, epistaxis, or even more serious bleeding). A common and relatively typical symptom of ALL is **bone pain**. The most diverse **neurological symptoms** can be with CNS infiltration. In about half of the cases, **lymphadenopathy** is present in the most diverse localizations, sometimes **hepatomegaly** or **splenomegaly.**

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Diagnostics

In the blood count there is periodically anemia and thrombocytopenia of varying degrees, the number of leukocytes can be increased, decreased, but also within the limits of the norm. With a differential leukocyte budget, young bone marrow precursor cells are present – **blasts.**

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

The basic diagnostic method is a microscopic examination of a smear of peripheral blood and especially 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 examination in the diagnosis of acute leukemia is **flow cytometry** of bone marrow or peripheral blood, which distinguishes ALL, AML and other rare types of acute leukemia.

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

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

Lumbar puncture is also performed with cytological and flowcytometric examination of the liquor for the risk of CNS infiltration by this disease.

Other now standard laboratory examinations necessary for proper risk stratification and treatment management are cytogenetic examination of karyotype and chromosomal aberrations using **FISH** (fluorescence in-situ hybridization) and a 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 below the limit of detection by microscopic methods may persist in the marrow.

Treatment

Treatment of ALL takes place in specialized hematooncological centers for patients of child or adult age. Combined regimens consisting of chemotherapy, immunotherapy, tyrosine kinase inhibitors, corticosteroids, radiotherapy and hematopoietic stem cell transplantation are used.

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

1. **Induction** – The most intensive part of the treatment aimed at inducing complete remission, i.e. destroying the entire tumor population detectable by microscopic examination in the 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 is administered in adults under hospitalization (in contrast, in children almost all treatment is carried out 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. Patients **at lower risk** – Several cycles of treatment of about 12 months, in adults in a combined outpatient and inpatient regimen, in children on an outpatient basis.
    2. Patients **at higher risk** – These are patients with *BCR-ABL1*, *KMT2A-AF4*, baseline pronounced hyperleucocytosis, 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 transplantation of hematopoietic stem cells is performed** (see below).
3. **Maintenance therapy** – Outpatient treatment to reduce the risk of late relapses, lasts about 1-2 years. After allogeneic transplantation, it is usually not administered.

- **Palliative and symptomatic treatment** – For elderly patients unable to undergo more intense, toxic

curative treatment and for recurrent relapsed diseases where other treatment options have been exhausted.

- **Treatment of relapse or primarily resistant disease:**
  - Treatment of relapse or primarily resistant disease.
  - Monoclonal antibodies in B-ALL – **Blinatumomab** (bispecific anti-CD19/anti-CD3 antibody) and **inotuzumab ozogamicin** (anti-CD22 immunoconjugate and calycheamycin cytostatics).
  - Purine analogue of **nelarabine** in T-ALL.
  - Tyrosine kinase inhibitors of the 2nd and 3rd generation **dasatinib** and **ponatinib** in relapsed *Ph-positive* ALL.
  - **CAR-T lymphocytes** – Genetically modified T-lymphocytes of a patient with an inserted gene for the chimerical antigen receptor (CAR) directed against one of the antigens on the surface of the blasts, most commonly CD19. Highly effective and costly treatment with specific toxicity (cytokine release syndrome and neurotoxicity syndrome associated with immune effector cells). 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 **allogeneic hematopoietic stem cell transplantation** after induction of the 2nd complete remission, otherwise the chance of maintaining long-term remission is basically zero. In elderly patients unable to undergo an allogeneic transplant, relapse treatment is always palliative treatment.

- **Allogeneic transplantation of hematopoietic stem cells** – The source of cells today are almost always peripheral stem cells leached into the peripheral blood by mobilization of G-CSF (granulocytic colony stimulating factor). Stem cells taken by puncture directly from the bone marrow are rarely used today for 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 preparatory regimen may be **myeloablative** (in younger patients) or with **reduced intensity/non-myeloablative**, for older patients). A stem cell donor may be an HLA-identical sibling, a HLA-identical unrelated donor from the registry, or an alternative non-matching donor (an unrelated donor with a partial match or a haploidentical donor from the patient's family). The age limit of feasibility of allogeneic transplantation is about 65-75 years of age, but each patient is assessed individually on the basis of biological age, comorbidities, previous complications of treatment and the availability of a suitable donor.
- **Autologous transplantation of hematopoietic stem cells** – Routinely it is no longer 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 for ALL is very variable and depends on many factors, especially age and risk stratification. With current treatment, complete remission in more than 95% and long-term survival in almost 90% can be achieved in children. In adults, the situation is less favorable. Patients under 55 years of age manage to induce complete remission 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 with palliatives have a poor prognosis with median survival in the order of weeks to several months.

Links

Related articles

- Leukemie
- Akutní myeloidní leukemie
- Akutní promyelocytární leukemie
- Chronická myeloidní leukemie
- Chronická lymfocytární leukemie
- Vlasatobuněčná leukemie

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