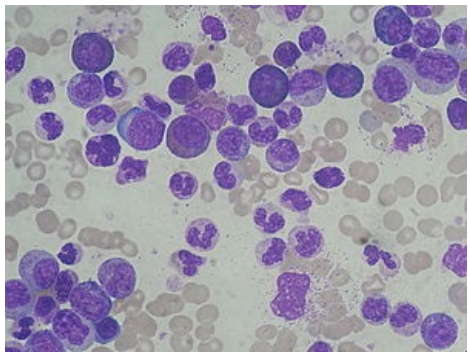
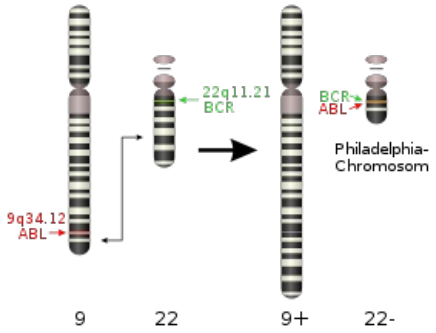
Chronic myeloid leukemia

Chronic myeloid leukemia	
Localization	bone marrow
Prevalence in the Czech Republic	increasing due to targeted therapy
Incidence in the Czech Republic	1,2/100 000
Maximum incidence	60-65
Key mutation	(9;22)(q3.4;q1.1) Philadelphia chromosome
Therapeutic modalities	chemotherapy, biological therapy



Predominance of granulopoiesis elements



Philadelphia Chromosom

Chronic myeloid leukemia (CML) is a malignant clonal disease of hematopoiesis characterized by the presence of a specific acquired genetic abnormality - the **Philadelphia chromosome** (Ph-chromosome), which arises from the t(9;22) translocation. It is responsible for the uncontrolled proliferation of hematopoietic cells of the myeloid lineage, with leukocytosis predominating. It accounts for about 15-20% of newly diagnosed leukaemias, the incidence in the Czech Republic is **1.2/100 000 inhabitants** per year. The median age of diagnosis is around **60-65 years**, with a rare occurrence in children.

A characteristic feature of cancer cells in CML is presence of the **Philadelphia Ph chromosome** [1] translocation of part 9 of the Chromosome – carries protooncogene c-abl) to the 22nd chromosome (bcr gene) – a fusion bcr/abl gene is produced, which can be demonstrated even in cases where the Ph-chromosome cannot be determined (about 10% CML). The proliferation of the pathological clone gradually displaces normal hematic formation and leads to a multiple increase in the total granulocyte mass, the presence of a Ph-chromosome leads to further mutations in the formation of malignant clones with greater proliferation activity (de-differencing of malignant cells) – these new populations gradually replace the original "benign" leukemia clone and eventually completely prevalent – the so-called "benign" leukemia clone. blast reversal (course as with AML with massive blast leaching – more than 30% of monoblasts in the marrow or blood, bleeding, susceptibility to infections, anemia).

Causes

CML is caused by a **reciprocal translocation** of parts of the long arms between chromosomes 9 and 22. On the resulting Philadelphia chromosome, the fusion gene BCR-ABL1 is located. This gene produces the pathological, constitutively activated tyrosine kinase Bcr-Abl, which is responsible for the uncontrolled proliferation of hematopoietic cells and their reduced response to proapoptotic signals. The actual cause of the Philadelphia chromosome is unknown.

Symptoms

The disease is characterized by 3 phases: chronic (CF, 95% of diagnoses), accelerated (AF) and blastic (BF). The intensity of symptoms usually increases with the progression of the phase. The symptoms themselves are non-specific:

- fatigue, increased sweating, weight loss,
- subfebrile to febrile,
- left lower back pain, feeling full after eating,
- splenomegaly, possibly hepatomegaly,
- rarely haemorrhage and manifestations of leucostasis (dyspnoea, priapism).

Leukostasis syndrome

Hyperleukocytosis is a leukocyte count greater than 100 000/μl. In CML patients, symptoms of leukostasis are only apparent at values of around 400 000/μl. High leukocyte counts lead to increased blood viscosity, obstruction of capillaries and subsequent hypoxia or bleeding when they rupture. This manifests itself in various neurological symptoms, visual disturbance with retinal haemorrhage, dyspnoea, ischaemia of other organs or priapism. In patients with hyperleukocytosis and manifestations of leukostasis, we perform **leukapheresis and cytoreduction** (hydroxyurea) to prevent or alleviate these symptoms and complications. Adequate hydration is necessary at the outset.

Around 50% of patients are asymptomatic and the disease is usually detected incidentally.

Diagnostics

In the blood picture, typically leukocytosis with a leftward shift in neutrophils, intermediate developmental forms of granulocytes (myelocytes, metamyelocytes) eosinophilia, basophilia. Often thrombocythaemia, more rarely thrombocytopenia, polyglobulia or anaemia. In the accelerated and blastic phase, myeloid blasts are present in the peripheral blood, similar to acute myeloid leukaemia.

Cytogenetic examination of bone marrow aspirate demonstrates the presence of **Ph-chromosome**, fluorescence in situ hybridization demonstrates the presence of **BCR-ABL1** gene, RT-PCR confirms the positivity of BCR-ABL1 transcript.

Chronic phase:

- Does not meet criteria for accelerated or blastic phase.

The **accelerated phase** must meet one or more of the following criteria:

- 10-19% blasts in blood or marrow,
- ≧20 % basophils in blood,
- persistent thrombocytopenia (not caused by treatment) or unresponsive thrombocytosis,
- increasing leukocyte count and enlarging spleen,
- clonal evolution.

The **blastic phase** must meet one or more of the following criteria:

- ≧20% blasts in blood or marrow,
- Extramedullary blastic proliferation.

After diagnosis, biochemical examination of liver, pancreatic, and renal function, lipid profile, glucose, mineralogram, ECG, echocardiography, and spleen size determination are appropriate to select the appropriate drug and calculate a prognostic score.

The prognostic score (ELTS) for patients in the chronic phase should be calculated before starting therapy from age, spleen size, basophil, eosinophil, blast and platelet counts.

European Leukemia Net: The EUTOS long-term survival (ELTS) score (https://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html)

Microscopic image

Bone marrow

- Hypercellular marrow with a pronounced predominance of granulopoetic elements, oppression of erythropoiesis,
- the representation of megakaryocytes highly variable (CML can be divided into CGL - granulocytic and CGML - granulocytomegakaryocytic),
- changes in stroma include the appearance of special collecting macrophage (called gaucheroid cells) or macrophages with hexagonal crystalloid formations in the cytoplasm (macroscopically the bone marrow is pyoid – i.e. similar to pus),
- In forms with the multiplication of megakaryocytes, the multiplication of reticular fibers to myelofibrosis often leads to secondary thinning of bone beams.

Extramedullary tissue

- **Spleen** – sinuses infiltrated by elements of granulopoiesis, or megakaryocytes, **pronounced splenomegaly** (up to 10 kg – the most pronounced enlargement of the spleen is precisely in CML),
- **liver** – infiltration mainly in sinuses (unlike CLL, when infiltration is mainly in portobilia),
- **nodules** – diffuse infiltration by leukemia cells (only in late stages).

Schéma translokace|thumb|200px

Finding in peripheral blood

- High leukocytosis (50-250×109/l), *Leukemic hiatus* typical of AML
  - is missing (all the developmental stages of granulocytes are found in the differential).

    A high number of leukocytes increases blood viscosity, which causes a decrease in blood flow to blood arrest (leukostasis

- It differs from the leukemia reaction (a condition resembling leukemia, when there are few mature white blood cells in the blood due to infection) with low leukocytic AF activity and the presence of a Ph-chromosome.

- **The number of platelets** can be normal, increased and decreased.

Clinical manifestations

Clinically, three stages of the disease are distinguished: the chronic phase, the acceleration phase, the blast reversal phase. Symptoms of CML are nonspecific, include weight loss, temperature, sweating, loss of appetite. Up to 40% of cases are diagnosed randomly, based on blood counts. Splenomegaly is often present from physical examination (in more than 50% of cases). In case of successful therapy, the size of the spleen returns to normal. Severe anemia is rarely present, on the contrary, we often find thrombocytosis.

Therapy

The mainstay of CML treatment is **tyrosine kinase inhibitors (TKIs)**. The goal is to achieve a profound molecular response, defined as a 4-5 log decrease in BCR-ABL1 transcript levels relative to standardized levels.

The first-line treatment is either one of the first-generation TKIs **imatinib** or one of the second-generation TKIs **nilotinib, dasatinib or bosutinib**. The choice of a particular TKI depends on the risk of CML and the patient's comorbidities. The presence of a T315I mutation in the ABL kinase domain is an indication for the use of the 3rd generation TKI **ponatinib**. Each of the available TKIs has efficacy on a different spectrum of ABL kinase domain mutations and different adverse effects. Therefore, it is always necessary to select the most appropriate agent for a particular patient and at a particular stage of disease.

Second-line treatment, in the event of the development of resistance to a given TKI or disease progression, consists of the administration of another suitable TKI, preferably after analysis of ABL kinase domain mutations.

After failure of the second line, a third TKI may be administered in low- and intermediate-risk patients, while **hematopoietic stem cell transplantation** is indicated in high-risk patients. If transplantation is not possible, **interferon-alpha** is administered.

For patients diagnosed in the accelerated and blastic phase, a TKI (usually 2nd or 3rd generation) is administered. If an optimal response is not achieved or if there is a shift to AF/BF during treatment, hematopoietic stem cell transplantation is indicated. AF and BF may be myeloid (more common) or lymphoid depending on blast differentiation. If the course is rapid and the number of blasts is high, one of the **intensive salvage chemotherapy regimens** is administered prior to transplantation, similar to the treatment of acute myeloid or lymphoblastic leukemia (FLAG, FLAG-IDA, HyperCVAD...).

Palliative cytoreduction with hydroxyurea is administered in patients who have exhausted all therapeutic options. This situation rarely occurs anymore.

The therapeutic effect is monitored by blood counts, cytogenetic testing at 3, 6 and 12 months and RT-PCR every 3 months. In patients in long-term deep molecular remission without previous treatment failure, gradual withdrawal of TKIs may be considered with close monitoring of disease status. TKI withdrawal and its conditions are currently the subject of clinical trials and expert discussions.

Links

Related articles

- Chronic lymphocytic leukemia
- Acute myeloid leukemia
- Acute lymphoblastic lekemia
- Hairy cell leukemia
- Philadelphia chromosome
- Imatinib

Sources

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