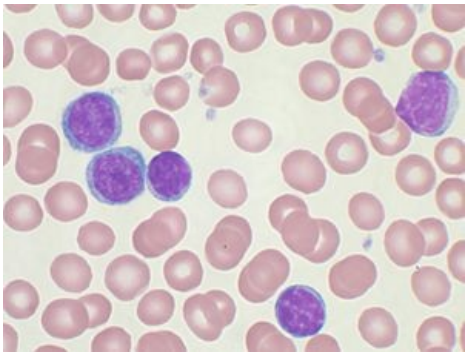
Chronic lymphocytic leukemia

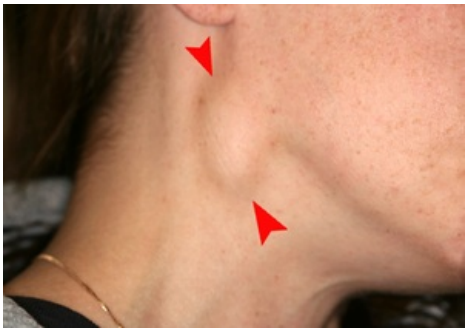
Chronic lymphocytic leukemia (CLL)	
Localization	bone marrow
Incidence in the Czech Republic	6/100 000
Therapeutic modalities	chemotherapy, immunotherapy, B-cell signalling inhibitors


Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disease with **low malignancy**. It's essence is clonal proliferation of malignant transformed mature lymphocytes (in 95 % cases its B-lymphocytes). These lymphocytes do not undergo apoptosis as fast as in their physiological form – gradual increase in the amount of lymphocytes is caused not only by uncontrolled proliferation, but mainly due to their inability to apoptose. In the pathogenesis of the disease there is an **increased expression of the gene bcl-2**, resulting in **inhibition of apoptosis of pathological lymphocytes**. Pathological lymphocytes are characterised by monoclonal surface Ig (proved by immunofluoresence) that are unable to respond to antigenous stimulus (level of antibodies in plasma is usually lowered, because pathological B-lymphocytes produce TGF-β inhibiting the proliferation of physiological B-lymphocytes, which causes an **increased risk of infection complications**, and may have an autoimmune development hemolytic anaemia and thrombocytopenia).

Chronic lymphocytic leukemia (CLL) is an indolent malignant lymphoproliferative disease characterized by clonal proliferation and impaired apoptosis of mature B lymphocytes with a typical immunophenotype. These cells subsequently accumulate in the blood, bone marrow, liver and spleen. It is the most common leukemia in the Western adult population, with an incidence of about 6/100,000 inhabitants per year. It typically occurs in the elderly population, with a median age at diagnosis of 72 years. The incidence increases with age.

The form of CLL without evidence of clonal lymphocytes in peripheral blood and bone marrow, with only involvement of lymph nodes or other organs, is called small lymphocyte lymphoma (SLL). According to the WHO classification, it is the same disease as CLL/SLL, and the treatment is the same as for CLL.


Regional spread of oral squamous cell carcinoma to the right jugulodigastic chain of lymph nodes zone IIa of the neck

Causes

The pathogenesis of CLL has not yet been fully elucidated. Changes at the chromosomal level (deletion 13q, deletion 11q, trisomy 12) and a number of minor mutations are likely to be involved, and a genetic predisposition within the family is also possible.

Pathology

Microscopical image

náhled|150px|vpravo|Bone marrow of an adult male with distinct lymphocytosis; lymphocytes − sparce pale cytoplasm, immature nucleolus

Bone Marrow

The leukemic infiltrate looks like **dispersed lymphoid nodules** and variously expressed infiltration in the septa (interstitial, reticular infiltration), but can even progress to massive infiltrate with replacing the original myeolopoiesis (adverse diagnostic feature).

Extramedullar tissue

1. **nodes** – **wiped out structure** monotonous lymphoid infiltration, sometimes with dispersed immature cells (so called paraimmunoblasts), infiltration of the nodes is obvious (unlike in CML);
2. **spleen** – infiltration **in sinuses** (red pulp), distinction between the red and white pulp is no longer evident
3. **liver** – infiltration **in the portobili** (in CML, the infiltrate is mainly in the sinuses).

Macroscopical image

Macroscopical **findings on the organs** are usually **less obvious** than in CML.

Main features:

- enlargement of nodes (generalized **lymphadenopathy** – cervical, axillary and inguinal nodes) a spleen (**splenomegaly**), in advanced stages the liver, prostate etc. are also infiltrated;
- **anaemia**;
- **thrombocytopenia**.

T-CLL is not morphologically different from **B-CLL** with the exception of Sézary syndrome, where the infiltration is extensive from tumour cells predominantly in the skin, the cells are big, with a broken down nucleus (cerebriform nucleus).

A variant of CLL is **prolymphocytic CLL**, where large lymphoid cells appear in the blood and bone marrow with distinct nucleoli.They are referred to as prolymphocytes and the prognosis of this state is **worse** than in the typical CLL.

Clinical part

Manifestations

Symptoms tend to be subtle and non-specific:

- symptoms of anaemia (fatigue, breathlessness), leukopenia (infection) or thrombocytopenia (increased bleeding),
- B symptoms - fever without evidence of infection, night sweats, weight loss,
- hepatosplenomegaly

Up to 70% of patients are asymptomatic at the time of diagnosis.

Clinical picture of the patient

CLL is a disease affecting mainly the **older age group** (more than 65 years), more commonly affects **males**. Patients are **asymptomatic** for a long time. Lymphocytosis can be an **accidental finding** during a preventive examination.

Further findings may include:

- lymphadenopathy, splenomegaly, hepatomegaly;
- infiltration of different areas of the body: retroperitoneum, mediastinum (nodes).

Examination methods

- **peripheral blood** − absolute lymphocytosis > $5 \cdot 10^9$/l lasting longer than 3 months, may also include anaemia and thrombocytopenia;
- **immunophenotyping** − determination of the characteristics of cells according to the receptors on their surfaces (CD19, CD23, CD38, ZAP-70);
- **Examination of the bone marrow** − usually is not necessary for the dtermination of the diagnosis but is done before the start of treatment;
- **cytologic examination** (deletions, trisomies) − present in up to 80 % of patients;
- **biochemical testing** − LDH, beta-2-microglobulin, thymidinkinase;
- X-ray of the chest (always);
- Ultrasound of abdomen − determination of adenopathies, hepatosplenomegaly;
- CT of chest, abdomen and the small pelvis − before start of tehrapy.

Diagnosis

The diagnosis of CLL is made on the basis of blood count and peripheral blood flow cytometry. The presence of ≧5x10^9/l clonal B lymphocytes is required. Morphologically, these are uniform mature lymphocytes with a round or oval nucleus and condensed chromatin. These cells are fragmented, and we also find disintegrated cellular remnants, so-called Gumprecht shadows, in the smear. Flow cytometry confirms the clonality and immunophenotype of the B cells. In addition to the universal B-cell antigens CD19 and CD20, typical CLL cells express CD5 and CD23, weakly CD79b and sIg (surface immunoglobulin) and are negative for FMC7 (Matutes' dg. criteria). Histological examination of lymph nodes and bone marrow is not necessary to establish the diagnosis of CLL, but is important in suspected transformation of CLL into a more aggressive lymphoid malignancy (Richter's syndrome), in atypical cell phenotype and in clarifying the etiology of possible anemia and thrombocytopenia.

Clinical stages and variants, prognosis

At diagnosis, the clinical stage according to Rai and Binet is determined on the basis of physical examination and blood count:

Stages according to Rai

0 - Lymphocytosis

I - Lymphocytosis + lymphadenopathy

II - Lymphocytosis + spleno/hepatomegaly

III - Lymphocytosis + anaemia (Hb < 110g/l)

IV - Lymphocytosis + thrombocytopenia (<100x10^9/l)

Stages according to Binet

A - < 3 affected lymph node groups

B - ≧ 3 affected lymph node groups

C - Anemia (Hb < 110g/l) or thrombocytopenia (<100x10^9/l)

Negative prognosis factors:

- short **LDT** (lymphocyte doubling time) < 12 months (time, in which the tumour population doubles);
- not mutated state of the heavy chains of immunoglobulins;
- elevated enzymes − LDH, ThK;
- surface markers CD38 and ZAP-70;
- cytogenetics − deletion of 17p;
- range of bone marrow infiltration > 35% of population is formed by tumour cells.

Richter syndrome is transformation to another more aggressive lymphoproliferation, most commonly diffuse large B-cell lymphoma (DLBCL), more rarely to others. Prognostically, this is a very unfavourable phenomenon. Significant elevation of lactate dehydrogenase (LD), rapid progression of lymphadenopathy (especially asymmetric), development of B symptoms or disease progression with ongoing therapy are suspicious. PET/CT may help to determine the extent of disease; extirpation of the nodule with histological examination is crucial. They are treated as aggressive lymphomas according to the respective histological type.

Translated with www.DeepL.com/Translator (free version)

Differential diagnosis

Conditions which may resemble CLL:

- prolymphocytic leukemia,
- hairy cell leukemia,
- lymphoma of small lymphocytes,
- monoclonal B-lmyphocytosis,
- splenic lymphoma.

Complications of CLL

Amongst the complications of CLL is the development of anaemia and/or thrombocytopenia, which may occur by 2 mechanisms:

1. **oppression** of the normal hematopoietic tissue by the influence of the expansion of the tumour process;
2. **autoimmune** − the production of antibodies against erythrocytes and/or thrombocytes (therapy − corticoids).

Therapy

As long as the CLL patient is asymptomatic, it remains untreated, but it is controlled. If it were to come to a progression of the disease, the treatment is initiated according to its clinical stage and prognosis (comorbidities). The signs of the progression of the illness are suddenly appearing symptoms (fast weight loss, fatigue, night sweats, febrile, short doubling time, appearance or worsening of the hepatosplenomegaly, signs of the progression of medullary oppression − anaemia, thrombocytopenia). Standardly a combination of treatments is used **FCR** (immunochemotherapy):

- **fludarabin** − purine analogue;
- **cyclophosphamide** − alkaline substance;
- **rituximab** − monoclonal antibody anti CD20.

According to the clinical stage, general state of the patient and prognostic factors we are able to choose from the following therapy scheme:

1. intensive therapy − FCR combination, if unsuccessful, one can also use the monoclonal antibody alemtuzumab (anti CD52);
2. easy therapy − FCR − lite, i.e. the same drugs, but smaller dosage;
3. palliative treatment − radiotherapy.

Treatment

In asymptomatic patients (Rai 0, Binet A), treatment is not initiated; we follow a "watch & wait" strategy. With only mild anaemia or thrombocytopenia, treatment may not be initiated and regular follow-up is recommended.

With moderately advanced disease (Rai I/II, Binet B), we only initiate treatment if there is evidence of CLL activity, if at least one of the conditions is met:

- progressive bone marrow failure with cytopenia,
- massive (over 6 cm) or progressive splenomegaly,
- massive (over 10 cm) or progressive lymphadenopathy,
- progressive lymphocytosis or LDT under 6 months,
- autoimmune anaemia or thrombocytopenia unresponsive to corticosteroids,
- presence of B symptoms.

Advanced disease (Rai III/IV, Binet C) is almost always an indication for initiation of treatment.

Treatment in patients without significant comorbidities

The first choice is the **FCR regimen - fludarabine, cyclophosphamide, rituximab** (anti-CD20 monoclonal antibody). The presence of a 17p deletion/mutation of the TP53 gene is an indication for treatment with inhibitors of B-cell signalling (**ibrutinib, idelalisib**). In relapsed or refractory CLL, **ibrutinib, idelalisib, venetoclax** (bcl-2 inhibitor) or a combination of anti-CD20 antibody (**rituximab, obinutuzumab**) with a cytostatic **(bendamustine, chlorambucil**) is administered. If the treatment response has lasted more than 3 years, first-line treatment can be repeated.

Treatment in patients with significant comorbidities

We can use a dose-reducing **FCR** regimen, combination of anti-CD20 antibody (**rituximab, obinutuzumab**) with a cytostatic (**bendamustine, chlorambucil**), **ibrutinib or idelalisib** in case of 17p deletion/mutation of TP53. In relapsed or refractory CLL, one of the above regimens is again administered, and if treatment with B-cell signalling inhibitors fails, **venetoclax** is administered. For stabilisation of autoimmune haemolytic anaemia or immune thrombocytopenia associated with CLL, immunosuppressive **RCD regimens** are most commonly chosen - **rituximab, cyclophosphamide, dexamethasone**. However, it is also administered to comorbid patients as part of the treatment of CLL beyond immune cytopenias.

Hematopoietic cell transplantation is the only CLL treatment with curative potential. However, it is burdened with a non-negligible peritransplant mortality and risk of post-transplant relapse. It is recommended for younger patients with relapsed/refractory CLL with 17p deletion/mutation of TP53 and a generally unfavourable clinical course.

Supportive therapy is primarily aimed at preventing or treating infectious complications. Depending on the intensity of the treatment regimen and the needs of the individual patient, antibiotics, antivirals, antifungals, immunoglobulin replacement, G-CSF, and vaccination (pneumococcal and influenza) are administered.

Some new drugs for CLL in clinical trials

B-cell signalling inhibitors: **acalabrutinib, zanubrutinib, duvelisib.**

CAR-T lymphocytes (genetically modified patient T-lymphocytes with affinity against a defined antigen expressed on the surface of malignant cells, usually CD19 and CD22 in B-lymphoproliferations).

Prognosis

CLL is a very heterogeneous disease and individual prognosis varies considerably. However, the 5-year survival rate is around 80% and a large proportion of patients live longer than 10 years. Although the introduction of B-cell signalling inhibitors and bcl-2 inhibitors in recent years marks a significant advance in the treatment of this disease, CLL remains incurable by conventional regimens. However, the time to progression is being extended and the quality of life of patients is improving significantly, with a number of new drugs being tested in clinical trials.

Links

Related articles

- Leukemia
- Acute lymphocytic leukemia
- Acute myeoloid leukemia
- Chronic myeloid leukemia
- Hairy cell leukemia
- Chronic lymphadenosis of marrow (slide)

External links

- Chronická lymfocytární leukemie + dif. dg. splenomegalie (https://int1.lf1.cuni.cz/file/5677/web-cll-splenomegalie.pdf) přednáška z Hematologie, I. interní klinika VFN
- Chronická lymfatická leukémie (https://www.stefajir.cz/?q=chronicka-lymfaticka-leukemie) článek na stefajir.cz
- Chronická lymfatická leukémie (http://www.fnbrno.cz/data/files/IHOK/CLL%20pro%20pacienty.pdf) informace

pro pacienty a jejich blízké (FN Brno)
- Hematologové z Brna vymysleli nový způsob léčby chronické lymfocytární leukemie (https://www.irozhlas.cz/neposouvat_-_veda/hematologove-z-brna-vymysleli-novy-zpusob-lecby-chronicke-lymfocytarni-leukemie_201101302126_kkrenova) článek na Rozhlas.cz
- Chronické lymfatické leukémie (https://zdravi.euro.cz/clanek/postgradualni-medicina/chronicke-lymfaticke-leukemie-126771) článek na zdravi.euro.cz

References

- BÜCHLER, Tomáš. *Speciální onkologie*. 2. vydání. Praha: Maxdorf, [2020]. Jessenius. ISBN 978-80-7345-651-1.
- DOUBEK, Michael, MAYER, Jiří (Eds.). Léčebné postupy v hematologii 2020. Doporučení České hematologické společnosti České lékařské společnosti Jana Evangelisty Purkyně. 1. vyd. 2020. ISBN 978-80-270-8240-7 (https://www.hematology.cz/wp-content/uploads/2021/08/Doporuceni_CHS_CLS_JEP-Cervena_kniha.pdf).
- Chronic Lymphocytic Leukemia: Diagnosis and Treatment (https://www.mayoclinicproceedings.org/article/S0025-6196(18)30154-X/fulltext)
- Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatmen (https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25595)t