MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

„NICOLAE TESTEMITANU" STATE UNIVERSITY OF MEDICINE AND PHARMACY

Musteata Vasile

CLINICO-BIOLOGIC PATTERNS, DIAGNOSIS AND MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

(methodical guidelines for students)

CHIȘINAU, 2021

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CONTENTS

LIST OF ABBREVIATIONS

CML – chronic myeloid leukemia
CD – cluster of differentiation
BM – bone marrow
FISH – fluorescence in situ hybridization
CT – computed tomography
ECOG – The Eastern Cooperative Oncology Group
WHO – Word Health Organisation
CBC – complete blood count
BCR – breakpoint cluster region
BCR-ABL1 – breakpoint cluster region-Abelson 1
JAK – Janus kinases
JAK2 – Janus kinase 2
CALR – calreticulin
MPL – myeloproliferativeleukemia
MPNs – myeloproliferative neoplasms
PMF – primary myelofibrosis
PV – polycythemiavera
ET – essential thrombocythemia
AML – acute myeloblastic leukemia
LDH – lactate dehydrogenase
RT-QPCR – reverse transcriptase quantitative polymerase chain reaction
ROS – reactive oxygen species
TERT– telomerase reverse transcriptase
TKIs – tyrosine kinase inhibitor
HSCT – hematopoietic stem cell transplantation
IFN α-2b – recombinant interferon alpha
OS – overall survival
RFS – relapse free survival

CLINICO-BIOLOGIC PATTERNS, DIAGNOSIS AND MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

Definition

Chronic myeloid leukemia (CML) represents a clonal tumor process of the hematopoietic system, which results from the malignant transformation of the pluripotent stem cell, while maintaining the differentiation property to all cell lines [2,6,7,8,30]. According to current specialized iterature sources, CML is characterized by uncontrolled multiplication of myeloid series cells, with an increase in circulating and total granulocyte mass, constituting 15-20% of all leukemia cases in adults, the most frequently recorded being chronic myeloproliferative neoplasia [2,3,8,17,29,30]. CML was presumably described and recognized as a distinctive nosological entity by Craigie D. in 1845 [9,17]. In 1865, the use of arsenic (Fowler's solution) in the treatment of CML was documented. The concept of myeloproliferative neoplasms was introduced by Dameshek W. in 1951 [10]. Dameshek W. was the first to describe the considerable overlap of PV, ET and PMF clinical and laboratory features, thus proposing that these, along with CML, may involve a spectrum of related diseases. He coined the term “myeloproliferative disorders” to comprise these related conditions [10].Over the last two decades, a significant progress has been made in the diagnosis and treatment of CML, especially related to the implementation of immunophenotyping, cytogenetic and molecular examinations, allogeneic stem cell transplantation and antineoplastic targeted therapy. Although the disease can be cured in many cases, it considerably affects the patients' quality of life and life expectancy. The patients with CML advanced stages and relapses may encounter a significant disease burden in terms of symptoms and negative effect on their life quality, productivity, and daily living activities.

Preface

These methodical guidelines comprise the basic topics necessary for medical students to make the diagnosis of CML, as well as elaborate treatment principles and personalized treatment strategies. The methodical guidelines constitute an effort to make the subject issues on CML available, thus being perceived by the students. The major objective is to support the students of the Faculties of Medicine and Public Health. There have been defined the notions that will allow enriching the knowledge related to this field , as well as will provide useful data at all steps of knowledge assessment. An appropriate attention will be paid to the clinical activity of the students at the patient's bed, when carrying out practical skills, tests and clinical cases on the given subject. In order to achieve a better understanding of the subject issues presented in this methodical guidelines, we opted for using graphical materials (tables, figures, and diagrams), images, clinical cases and control tests.

Duration of the seminar

The seminar lasts 5 hours.

The aim of the seminar

To study the epidemiological aspects, ethiology, pathogenesis, clinical features, laboratory tests and health care options applied for diagnosis of CML, synthesis of management options and personalized treatment strategies.

Objectives of the seminar

1. To build-up knowledge on the epidemiology, etiology and pathogenesis of CML;
2. To develop knowledge on the clinical, hematological, morphological, immunophenotyping, immunohistochemical, cytogenetic and molecular features of CML;
3. To acquire practical skills in CML diagnosis;
4. To build-up knowledge ondifferential diagnosis of CML;
5. To develop overall management principles and personalized treatment strategies in CML.

The seminar will be proceeded

1. On Hematology Discipline, at "Nicolae Testemitanu" SUMPh, in groups of students,by using study modules.
2. Within the Hematology units of the Hematology Department of the PMSI Institute of Oncology of the Republic of Moldova.
3. Within the Hematologycentresat the Consulting Diagnostic Centre of the PMSI Institute of Oncology of the Republic of Moldova.

Methods and Materials used for the seminar

Teaching methods to be used

Teaching methods and procedure, involved in the effective learning and achievement of the suggested objectives, are as following:

- presentation of the subject by formulation of definitions, description, explanation and demonstration;
- joint interactive discussion;
- problem-solving cases;
- data summarizing and synthesising.

Various forms of independent, frontal, group, interactive activities are used at the seminars.

Methods of evaluation

- questioning on the study issue;
- problem-solving situations;
- analysis of clinical cases;
- single choice and multiple choice tests;
- individual work;
- assessment of practical skills;
- taking exam.

Materials used at the seminar

Teaching materials such as tables, schemes, algorithms, digital images, international guidelines are used for broader learning of CML. Power Point presentations will bealso applied at the seminars.

Questions for students' self-training

1. Epidemiology and etiology of CML.
2. CML pathogenesis.
3. Clinical patterns, phases and complications of CML
4. CML diagnosis.
5. Hematological features of CML.
6. The value of bone marrow aspiration/biopsy in CML.
7. Prognostic scoring in CML.
8. The value of immunophenotyping and immunohistochemistry in CML diagnosis.
9. The value of cytogenetic and molecular examinations in CML diagnosis.
10. Differential diagnosis of CML.
11. Principles of management and treatment options inCML.
12. Evolution and prognosis of CML.

Epidemiology of chronic myeloid leukemia

CML morbidity increases with age, showing a maximum incidence in people aged between 35 and 65 (the mean age - 53 years), which denotes the predominant involvement of a working-age population [3,12]. The results of the published studies show that approximately 2.5% of cases with CML refer to the age group under 20 years [18], 7.4% - to those aged between 20 - 34 years and 33% - to the age groups under 40 years, which indicatesa ponderable rate among young patients [6,13,19]. The incidence of CML varies between 0.8 - 2.0 cases per 100000 population. The National Institutes of Health estimated the number of cases diagnosed *de novo* in the USA at 8950 and the number of deaths from this disease at 1080 in 2017. The total number of patients diagnosed with CML increased annually by 2% during 2007-2016, and the total number of deaths decreased annually by 1% during the years 2008-2017 [20]. The 5-year survival rate years increased from 22% in the mid-70s to 90% currently in patients undergoing continuous

therapy with generation 1 tyrosine kinase inhibitors [21].CML predominantly affects males, the ratio of men:women being 1.3- 1.7: 1.

Etiology of chronic myeloid leukemia

The cause of CML is not well known yet, thus inducing screening difficulties in this oncopathology. Irradiation (especially in high doses) is considered a favouring etiological factor. The arguments are of statistical origin: increased incidence in radiotherapy / radiology medical staff who worked without adequate protection, in patients with ankylosing spondylitis treated with radiotherapy and in the population of Hiroshima and Nagasaki after the atomic bomb explosion [4,11,26,27]. Cases of the development of CML after radiotherapy and / or cytotoxic medication for other neoplasms and in patients with renal transplantation under the long-term immunesuppressive therapy are reported. The studies carried out in the groups of shipyard workers in Portsmouth (UK) in 2005 indicated the increased morbidity by myeloid leukemias following long-lasting exposure to various solvents. There are reports of an increased incidence of leukemias, especially of CML in workers with long-term exposure to low benzene levels [16], in women from some USA states, where water has been contaminated with tri- and tetrachloroethylene [15]. Obesity is associated with the increased morbidity by CML [15,20,28]. Patients with CML have a high frequency of HLACw3 and Cw4 genetic markers. At the same time, there is no evidence and arguments that viruses serve as etiologic factor in CML. Unlike malignant lymphomas and other leukemias, hereditary predisposition is not identified as a risk factor in the development of CML [6].

Pathogenesis of chronic myeloid leukemia

CML was the first malignant neoplasm identified in association with chromosomal aberration [12]. In 1960, US scientists G. Nowell and D. Hungerford identified translocation t(9;22)(q34;q11) or the Philadelphia chromosome in patients with BM cells in CML [6]. The Philadelphia chromosome (Ph-chromosome) is formed as a result of mutual transloca-

tion between the long arms of chromosomes 9 and 22, being highlighted in all dividing medullary cell series and is the cytogenetic marker of the disease, which provides a confident diagnosis and helps to assess the treatment outcomes.

Identification of the chimeric BCR-ABL fusion gene and the p210 transcript with tyrosine kinase activity outlines CML at the molecular level *(Figure 1, 2).* Due to the formation of the BCR-ABL1 fusion oncogene, the tyrosine kinase activity of the ABL1 portion increases, stimulating autophosphorylation and thus being a trigger factor of malignancy of the phenotype by modifying proteins, which participate in cell cycle regulation (Ras, MAPK, STAT, PI3K and MYC) [32, 33]. The breakpoint of the ABL1 gene occurs in exon 2. The oncogenic BCR comprises the breakpoint, which generates the translocation t(9;22)(q34; q11) in CML and affects exons e12-e16 (known as b1-b5) in the major region (M-bcr). The transcription product in the major region (M-bcr) – p210 protein, which is responsible for the classic CML phenotype is detectedin most CML patients. The p190 protein is formed following the rearrangement of the m-bcr region and reveals the production of the e1a2 transcript, which is less frequently determined in the CML. Less commonly, the transcription product p230 is also identified in the μ-bcr region, which is associated with the slow progression of the disease. Oncogenic BCR-ABL acts by mitogenic signaling, influences proteosome-mediated degradation, as well as Src, altering the signal transmission cascade, constantly maintainingthe cell growth. As a result, it increases the mitogenic activity of cells, disrupts the stromal adhesion of cells and inhibits apoptosis. Leukemic cells multiply, gradually expanding into the medullary cavities and reducing the clone of normal hematopoietic cells.

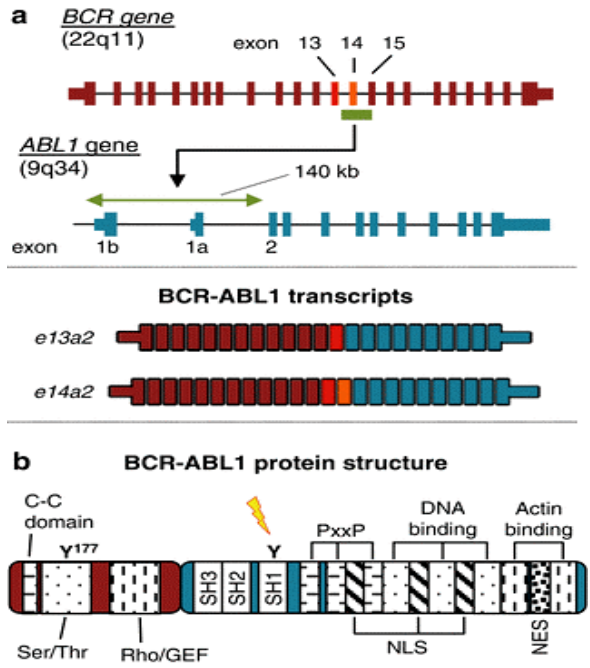

Figure 1. **Pathogenesis of CML [32]**

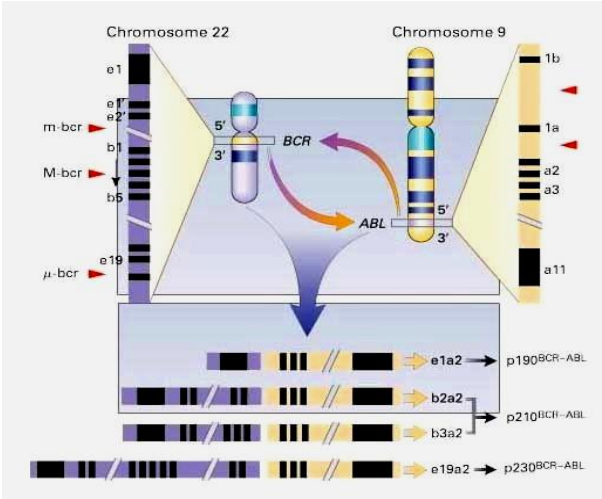

Figure 2. **Biology of CML [33]**

Clinical features, phases and complications of chronic myeloid leukemia

Most of current specialized literature sources and published studies, which are based on representative groups of cases, identified and registered all 3 clinical-evolutionary stages of CML (Table 1): the chronic (early and late), acceleration and acute ones[2,5,7,8,14,18,21].

According to the results of a recent Russian study, of 5655 patients enrolled in the CML register, the vast majority (93.1%) were diagnosed in the chronic phase, only 6.4% - in the acceleration phase and alower number (0,4%) – in the blast crisis. The aforementioned percentage distribution of CML patients by phases is relevant to the results of other international researchers, as well as of the local ones (chronic phase - 92.3%, acceleration - 7.7%) as referred to the field of chronic myeloproliferative neoplasms [8,18,19,21,36]. The data of the bibliographic references allow to summarize the improvements of the diagnostic approach in late chronic phase, by systematizing and grouping the clinical symptoms, the investigation results and by highlighting the following 4 syndromes in most patients: tumor intoxication, tumor proliferation (hepato- and splenomegaly), anemic and thrombotic-hemorrhagic complications [19,41]. The diagnosis is difficult to establish in reasonable terms in 15-30% of cases with asymptomatic evolution of the late chronic phase. Moreover, there are reported studies on late chronic phase associated with complications caused by hyperleuko- and thrombocytosis (spleen infarction, retinal edema, retinal microthrombosis, microthrombosis in the corpus cavernosum, stupor, ovarian apoplexy, neurosensory disorders, etc.) [1,37,38, 39]. The CBC shows a marked leukocytosis, which can reach values of 300-500 x 10^9/l, the shift to the left up to promyelocytes, myelocytes, metamyelocytes and a small percentage of blast cells. The average survival of patients without a specific treatment is 3-5 years in the chronic phase, and 1-2 years in the acceleration phase [29]. It may be considered of practical interest the clinical-evolutionary transformation of the late chronic phase into a blastic crisis in 20% of patients, without the development of the acceleration

phase, which requires a radical change in therapeutic management approach. According to contemporary conceptions and classifications, hepato- and splenomegaly are not considered as criteria for changing CML into advanced stages [2,41]. The clinical-hematological picture in the acute phase corresponds to the clinical-hematological picture of acute leukemia, followed by infectious and hemorrhagic complications, manifesting itself in regard to the morphological and immunophenotypic type of the blast crisis: myeloid (50-80%), lymphoid (20-30%) or undifferentiated (≤ 25%). The average survival of patients with the acute phase varies between 3-6 months, being associated with a less unfavourable immunocompromised status and prognosis in the lymphoblastic crisis, which justifies the major importance of early diagnosis of CML, especially in the current epidemiological context.

Table 1

Classification of chronic myeloid leukemia according to its phases [6,12,17]

Criteria	Chronic (early and late)	Acceleration	Acute (blast crisis)
Splenomegaly	controllable	persistent, progressive or refractory	persistent, progressive or refractory
Extramedullary involvement	---	---	Present
Blast cells in the BM aspirate (%)	≤ 10	≥ 10	≥ 20
Basofils + eosinofilsin the BM aspirate (%)	≤ 20	≥ 20	
Thrombocyte count (10^3/μL)	within the normal limits orcontrollable	uncontrollable thrombocytosis ≥ 1000 or persistent thrombocytopenia unrelated to therapy< 100	Persistent thrombocytopenia < 100
Leukocytecount (10^3/μL)	controllable	persistent, refractory leukocytosis or its doubling in 5 days	---

Cytogenetic patterns	clonal evolution	clonal evolution, new chromosomal aberrations (2ndPh, trisomy 8, iso-chromosom 17q, trisomy 19, complex karyotype oraberrations 3q26.2)	polyclonal evolution
Anemia	---	Refractory	Refractory
Provisional criterionof response to TKIs		hematological, cytogenetic and molecular indicators of resistance to 2 consecutive TKIs, the occurrence of 2 and more mutations in the BCR-ABL1 gene during therapy with TKIs	

Diagnosis of chronic myeloid leukemia

The milepost of diagnosis is leukocytosis with basophilia and shift up to the immature granulocytes, mostly metamyelocytes, myelocytes and promyelocytes, and scanty or occasional myeloblasts [14,33]. Severe anemia is uncommon. Thrombocytosis is frequent. Complete and differential blood counts, as well as BM examination are very important for the distinction between chronic, accelerated and acute phases. The diagnosis must be attested by cytogenetics detecting chromosomal translocation t(9;22)(q3.4;q1.1), and by RT-PCR detecting BCR-ABL transcripts. Cytogenetics must be performed by chromosome banding analysis of BM cell metaphases. If BM cells cannot be retrieved, chromosome banding analysis may be replaced by interphase FISH of blood cells, applying dual color fusion probes that allow the determination of BCR-ABL+ nuclei.

Hematological features of chronic myeloid leukemia

The CBC shows marked leukocytosis, which can reach values of 300-500 x 10^9/l, the shift to the left up to promyelocytes, myelocytes, metamyelocytes and a small percentage of blast cells [33]. Eosinophilia

is common, and absolute basophilia is usually present. Absolute monocytosis is uncommon and, if present, usually associates with the e1a2 breakpoint. Sometimes, patients may present a marked thrombocytosis with only mild leucocytosis. The acceleration phase is characterized by an increased myeloblast percentage in the peripheral blood or BM, as well as growing leucocytosis, basophilia or thrombocytosis, despite the ongoing therapy. Thrombocytopenia, unrelated to therapy, may indicate progressive marrow failure. The hematological patterns in the acute phase correspond to those in acute leukemia, manifesting itself in regard to the morphological and immunophenotypic type of the blast crisis: myeloid (50-80%), lymphoid (20-30 %) or undifferentiated (≤ 25%).

The value of the bone marrow aspiration and biopsy in diagnosis of chronic myeloid leukemia

In chronic CML phase, the BM is commonly hypercellular as a result of a significantly increased myeloid proliferation [12,19,24,33]. Myeloid maturation is normal or slightly left shifted, and blast cells usually don't exceed 5%. The myeloid/erythroid ratio is significantly increased and megakaryocyte numbers may be either decreased or increased compared to the normal BM; small and hypolobated forms are common. The increased reticulin fibres are observed in 30% of cases and correlate with larger spleen size. Pseudo-Gaucher cells and "blue sea" histiocytes may be seen secondary to the increased numbers of phagocytic cells amidst increased cell turnover. Although currently rarely used, the leucocyte alkaline phosphatase reaction using naphthol-ASD-chloroacetate esterase usually results in decreased staining in CML neutrophils, but increased staining with reactive neutrophilia. Acute phase is characterized by rapidly rising blast counts and BM failure as a result of uncontrollable growth of myeloid precursors with absence of maturation or differentiation. Morphologically, blast crisis is indistinguishable from other cases of acute leukaemia. In ≈70% of reported cases the blast cells are of myeloid lineage by morphology and

immunophenotype, and may exhibit antigens associated with granulocytic, monocytic, megakaryocytic or erythroid differentiation.

Risk stratification and prognostic scoring in chronic myeloid leukemia

In order to evaluate the CML prognosis and develop personalized treatment tactics, the risk score should be estimated according to Socal, EURO and EUTOS (Table 2)**[**14,17,18**]**. The EUTOS risk score is simpler, and has a greater prognostic value inimatinib-treated patients than Sokal and EURO. In all three systems the spleen is measured by manual palpation and expressed as maximum distance below costal margin. Complete and differential blood counts are importantfor the calculation of a prognostic risk.

Table 2

Risk stratification and prognostic scoring in chronic myeloid leukemia in regard to Socal, EURO and EUTOS systems [14**]**

CriteriaSocal	**EURO**	**EUTOS**	
Age (years)	0.116 (age—43.4)	0.666 when age >50	NA
Spleen size (cm)	0.345 × (spleen—7.51)	0.042 × spleen	4 × spleen
Platelet count (×109/l)	$0.188 \times [(\text{platelet}/700)^2 - 0.563]$	1.0956 when platelet ≥1500	NA
Blood blast cells (%)	0.887 × (blast cells—2.10)	0.0584 × blast cells	NA
Blood basophils (%)	NA	0.20399 when basophils >3%	7 × basophils
Blood eosinophils (%)	NA	0.0413 × eosinophils	NA
Relative risk	Exponential of the total	total × 1000	Total
Low	<0.8	≤780	≥87
Intermediate	0.8–1.2	781–1480	NA
High	>1.2	>1480	>87

The value of immunophenotyping and immunohistochemistry in diagnosis of chronic myeloid leukemia

Immunophenotyping of leukemic cells (with a score of a phenotype indicator > 1) is mostly applicable and resultant in the advanced stages [29]. Ph-chromosome+ colony-forming cells adhere less to fibronectin (and to BM stroma) than their normal counterparts do. Adhesion is promoted as a result of restoration of cooperation between activated integrins

and the altered epitopes of CD44. CML granulocytes have decreased and altered binding to P-selectin because of modification in the CD15 antigens. The expression of the phenotype CD13, CD33, CD34, CD117 is found in blast cells in the myeloblastic crisis. TERT is the catalytic subunit, the expression of which is closely correlated with telomerase activity. In CML CD34+ cells containing BCR-ABL, the expression of TERT is significantly lower than in normal CD34+ cells, consistent with accelerated shortening of telomeres in CML cells. Blasts in the remaining 25–30% of cases commonly express lymphoid antigens of B lineage. The acute B-cell lymphoblastic phase is usually confirmed by the expression of the immunophenotype CD19, CD20, CD22. The immunophenotype CD5, CD8, CD10 assesses the T-lymphoblastic crisis. According to the Recommendations of the European Group (EuroFlow Group) for Immunological Classification of Acute Leukemias the summary score over 2 points is necessary for the determination of the cell line [40].

The value of cytogenetic and molecular examinations in diagnosis of chronic myeloid leukemia

The CML diagnosis is based on detection of the Ph chromosomevia the cytogenetic analysis, or the BCR–ABL1fusion genewith RT-QPCR (also known as RQ-PCR, qRT-PCR or QPCR), in the context of compatible blood and BM morphology [30, 33]. Both cytogenetics and RQ-PCR (see below) offer complementary information and thus should be performed as a routine diagnosis. The Ph-chromosome was first linked to CML in 1960 by Nowell and Hungerford in Philadelphia (USA). Rowley in 1973 showed this to be a result of a mutual translocation between the long arms of chromosome 9 and 22. The translocation is carried by the leukemic stem cell population, thus both myeloid and lymphoid progenitors may carry t(9;22) in affected individuals. The translocation t(9;22)(q34;q11) is known to fuse the BCRand ABL1genestogether. The resulting BCR-ABL1fusion gene encodes a constitutively active tyrosine kinase that is central to the pathogenesis of Ph-chromosome+leukemias. Variant translocations, where BCR–ABL1 resides on a third chromoso-

me, are seen in≈ 5–10% of patients and may be cryptic, discernible only with FISH analysis. The ABL1breakpoint is almost invariably located in the intron between exons 1 and 2, whereas the *BCR* breakpoint usually occurs in an intron between exons 13–15. The resulting fusion transcripts are named e13a2 and e14a2 transcripts (previously known as b2a2 and b3a2); both may coexist in one individual due to alternate splicing. These transcripts encode fora 210 kDa protein product (p210). The RT-QPCR revealsp210 transcript of the BCR-ABL chimeric gene in all cases, with the range of 4.49-100% and a mean value of 74.73±3.21% [34].A breakpoint immediate downstream of the first BCR exon produces the e1a2 transcript, which encodes the p190 BCR–ABL1 protein. This is more commonly seen in Ph+acute lymphoblastic leukemia and is less frequent in CML. Uncommonly, the BCR breakpoint occurs between exons 17–20, leading to the larger p230 protein from the e19a2 transcript, associated with amore prominent neutrophilia and thrombocytosis. BCR–ABL1 also leads to genomic instability and facilitates disease transformation through accumulation of subsequent genetic lesions. DNA damage, such asdouble-stranded breaks, are mediated through increased ROSgenerated by BCR–ABL1.

Differential diagnosis of chronic myeloid leukemia

The differential diagnosis of CML should be carried out along with other pathologies, evolving with splenomegaly, leukocytosis, thrombocytosis and shift to the left of the leukocyte formula:

- Myeloid type of leukemoid reactions in malignant neoplasms (metastatic carcinoma), infectious and inflammatory pathologies (in the early chronic phase of CML);
- PMF (in the late chronic phase of CML);
- Chronic myelomonocytic leukemia (in the late chronic phase of CML);
- Acute leukemia (in the accelerated and acute phase of CML).
- Mercury poisoning;
- Severe acute hemolysis.

In myeloid type of leukemoid reactions, blood picture may resemble either acute myeloblastic leukaemia or CML. Marked neutrophilic leucocytosis with presence of premature white cells of all stages (from myeloblasts to segmented neutrophils) may imitate the early chronic phase of CML. The patient's performance status corresponds to the severity degree of the underlying disease. Basophil-eosinophil association is absent in the peripheral blood. The activity of leukocyte alkaline phosphatase is decreased in neutrophils. The peripheral blood and BM are dismissive of demonstration of Ph chromosome by cytogenetic analysis and BCR–ABL1fusion gene by RT-QPCR.

The clinical picture of PMF is variable. As in CML, approximately 30% of patients may be asymptomatic or oligo symptomatic at time of diagnosis, the disease being detected occasionally due to splenomegaly and changes in the blood count. Most patients may present splenomegaly or splenomegaly and hepatomegaly, progressive anemia, constitutional (fever, night sweats) or hypercatabolic (weight loss, anorexia) symptoms. Relevant changes in the blood count include moderate leukocytosis, with deviation to the left to myelocytes, metamyelocytes, and solitary blast cells. Hemoglobin levels and erythrocyte counts may be low, within normal ranges, or rarely increased (Vaughan type). The presence of erythroid and myeloid precursors in the peripheral blood (leucoerythroblastic picture) is common. The diagnosis of PMF is based on the results of histopathological examination of the BM and molecular-genetic investigations for the detection of JAK2, MPL or CALR mutations.

Acute myeloblastic leukemia is a hematological malignancy resulting from a clonal proliferation and accumulation of blast cells in the BM and peripheral blood. AML may be manifested by the following syndromes: anemic, hemorrhagic, proliferation and infectious complications. The diagnosis of AML requires morphology, cytochemistry, immunophenotyping, cytogenetics and molecular genetics (PCR, FISH) of the peripheral blood and BM specimens [35].Blast cells count in the BM aspirate is $\geq$ 20%.The most favourable types of AML are those with the chromosomal translocationst (8;21)(q22;q22), inv (16) (p13.1q22) or

t(16;16)(p13.1;q22). The somatic mutations of the genes FLT3 (a receptor tyrosine kinase), NPM1 (nucleophosmin) or CEBPα (a transcription factor) have been identified as important diagnostic and prognostic factors.

Principles of management and treatment options in chronic myeloid leukemia

The treatment of CML has advanced considerably over the last 2 decades. The main goals of CML management include reducing myeloid cell proliferation and decreasing the size of the spleen, obtaining complete clinico-hematological response, complete cytogenetic response, major (optimal) or complete molecular response, prevention of relapses, physical rehabilitation of patients and their social reintergration. Taken into account the clonal conception of pathogenesis of hematological malignancies, TKIs, chemo- and/or immunotherapy are considered as the treatment of choice for CML, followed by the allogeneic HSCT in case these are not effective. The CML evolution, treatment outcomes and prognosis have essentially improved after the development of the "targeted" therapy - TKIsin 1996, which block the constant activity of the BCR-ABL1 fusion gene [13]. Allogeneic HSCT remainsan effective therapeutic option, with a potential of recovery, especially in cases of resistance to TKIs [22,29]. Recombinant interferon alpha (IFN α-2b) can still be considered a valid treatmentapproach, contributing to the major cytogenetic response in 40% of patients and a complete cytogenetic response in 25% of patients. A complete clinical-hematological response can be obtained in 81% of cases in the chronic phase of CML while administering IFN α-2b [3,24,30]. The OS of patients treated over 5 years with IFN α-2b is 57%, showing a higher survival rate compared to the patients treated with chemotherapy (42%) [24]. The combination of IFN α-2b with Cytarabinum increases the rate of complete cytogenetic response up to 35%.

CML treatment may be performed both in outpatient and inpatient departments, as well as in the specialized hematology units, which

depends on the clinico-evolutionary phase of the disease and the presence of complications.

At the 1st step, in order to reduce myeloid proliferation and the spleen size, the following curative options are used, according to the phase:

– Early chronic phase: single-agent chemotherapy with Busulfanum - 2 mg 1–3 times a week; "targeted" therapy with Imatinibum - 400 mg daily, Nilotinibum - 600 mg daily, Dasatinibum - 100 mg daily, Bosutinibum - 500 mg daily or Ponatinibum - 45 mg daily.

– Late chronic phase: single-agent chemotherapy with Busulfanum– 4–6 mg daily; single-agent chemotherapy with Hydroxicarbamidum - 2–4 g daily; "targeted" therapy with Imatinibum 400 mg daily; "targeted" therapy with Nilotinibum–600 mg daily (as first-line treatment) or 800 mg daily, Dasatinibum - 100 mg daily, Bosutinibum - 500 mg daily or Ponatinibum - 45 mg daily.

– Acceleration phase: combined chemotherapy with Mercaptopurinum - 50–100 mg daily + Hydroxicarbamidum - 2 g daily or Mercaptopurinum - 50–100 mg daily + Busulfanum - 4–6 mg daily; single-agent chemotherapy with Cytarabinum - 20 mg / m^2 daily, 14–21 days; "targeted" therapy with Imatinibum- 600 mg daily, Nilotinibum - 800 mg daily, Dasatinibum - 140 mg daily, Bosutinibum - 500–600 mg daily or Ponatinibum–45 mg daily.

– Acute phase: combined chemotherapy according to the treatment programsfor acute leukemias depending on the morphological type and immunophenotypic profile of the blast crisis; "targeted" therapy with Imatinibum - 800 mg daily, Dasatinibum - 140 mg daily, Bosutinibum - 500–600 mg daily or Ponatinibum - 45 mg daily.

At the 2nd step of treatment, in order to obtain complete clinico-hematological response, complete cytogenetic response and optimal or complete molecular response, the following treatment options should be performed depending on the phase:

– Chronic phase, including that one obtained as a result of transformation from the treated acceleration and acute phases: IFN α-2b - 5 000

000 IU/m^2 daily; IFN α-2b - 5,000,000 IU/m^2 daily + Cytarabinum - 20 mg/m^2 daily (10 days per month); "targeted" therapy with Imatinibum - 400 mg daily; "targeted" therapy with Nilotinibum -600 mg daily (as first-line treatment) or 800 mg daily, Dasatinibum - 100 mg daily, Bosutinibum - 500 mg daily or Ponatinibum - 45 mg daily (in cases of resistance to Imatinibum, Nilotinibum or Dasatinibum).

– Acceleration phase: IFN α-2b 5 000 000 IU/m^2 daily + Cytarabinum 20 mg/m^2daily (10 days per month); "targeted" therapy with Imatinibum - 600 mg daily, Nilotinibum - 800 mg daily, Dasatinibum - 140 mg daily, Bosutinibum - 500–600 mg daily or Ponatinibum - 45 mg daily.

– Acute phase: combined chemotherapy according to the treatment protocolsfor acute leukemias depending on the morphological type andimmunophenotypic profile of the blast crisis; "targeted" therapy with Imatinibum - 800 mg daily, Dasatinibum - 140 mg daily, Bosutinibum - 500–600 mg daily or Ponatinibum - 45 mg daily.

At the 3rd step, in order to prevent CML relapse, the available management options include:

– maintenance therapy with IFN α-2b – 5 000 000 IU/m^2 daily;

– maintenance single-agent chemotherapy with Busulfanum - 2 mg 1–3 times a week or Hydroxicarbamidum - 0.5–1 g daily / over a day in the chronic phase of CML in cases of medication axed only on obtaining the clinico-hematological response;

– reinduction / combined chemotherapymaintenance with Hydroxicarbamidum- 0.5–1 g daily + Cytarabinum - 10–20 mg/m^2 daily for over 10 days per each month, in the chronic and acceleration phases of CML;

– "targeted" therapy with Imatinibum - 400–800 mg daily depending on the CML phase;

– "targeted" therapy with Nilotinibum - 600–800 mg daily, Dasatinibum - 100–140 mg daily, Bosutinibum - 500–600 mg daily or Ponatinibum - 45 mg daily depending on the CML phase:

– reinduction combined chemotherapy is performed according to the protocols for treatment of acute leukemias in the acute phase of CML.

Allogeneic HSCT can be performed in all phases of CML in cases of a response failure to chemo- and immunotherapy, if the HLA-compatible donor is available. After the "targeted" therapy with Imatinibum, allogeneic HSCT should be considered as a treatment option of choice in the absence of a complete hematological, cytogenetic and molecular response, after 3, 12 and 18 months respectively [2,5,7,14,22,23,30, 41].

Splenectomy is currently not considered a valid and standard treatment option in the chronic phase of CML because it does not prevent the development of the acute phase. There are some published studies on performing splenectomy in patients with spleen rupture associated with hemodynamic instability [25] and massive splenic infarction in cases of persistent uncontrollable symptoms and drug complications [1]. Supportive hemotransfusion treatment is substitutional. In determining the indications for transfusion of erythrocyte or platelet concentrate, the main role belongs to the overall condition of the patient, the degree of expression of anemic and hemorrhagic syndromes. The transfusions of erythrocyte concentrate are mandatory in cases of decreased Hb levels below 8 g/dL, with somatic decompensation. The prophylactic platelet concentrate transfusions are indicated during cytoreduction antineoplastic therapy, in thrombocytopenia $<10x10^3/\mu L$, even if the hemorrhagic syndrome is not common.

Criteria for evaluation the therapeutic response:

– Complete clinico-hematological response: regression of splenomegaly, normalization of CBC with leukocyte count $<10x10^9/L$, platelet count $<450x10^9/L$, basophils <5%, absence of immature granulocytes;

– Partial clinico-hematological response: persistent splenomegaly, but <50% reduction from pre-treatment assessment, presence of imamture granulocytes, platelet count <50% of pre-treatment assessment, but $>450x10^9/L$;

– Minimal cytogenetic response: 66 - 95% of Ph-chromosome+ BM metaphases;

– Minor cytogenetic response: 36 - 65% of Ph-chromosome+ BM metaphases;

– Major cytogenetic response: 1 - 35% of Ph-chromosome+ BM metaphases;

– Complete cytogenetic response: no Ph-chromosome+ BM metaphases;

– Major (optimal) molecular response: BCR-ABL fusion gene transcripts ≤ 0.1% (IS), or ≥3-log reduction of BCR-ABL mRNA;

– Complete molecular response: undetectable BCR-ABL fusion gene transcripts in 2 repeated blood samples or BCR-ABL mRNA undetectable by RT-PCR.

Patients receiving TKIs therapy should undergo RQ-PCR testing every 3 months for the first 2 years. After obtaining the complete cytogenetic response and the major/complete molecular response, the cytogenetic monitoring is recommended to be performed every 12 months, whereas the molecular monitoring by RT-PCR – every 6 months [19].It is a routine practice for some laboratories to examine only 20 metaphases per patient, resulting in a detection sensitivity for residual disease of ≈ 5%. FISH may be used as an adjunct to cytogenetics, when the Ph chromosome results from a cryptic translocation. FISH may also increase the sensitivity of residual disease detection [33].

Evolution and prognosis

Under the conventional chemotherapy, the average survival of patients with CML varies between 4-5 years, with 30% of them reaching 10 years [2]. At the same time, cases with a lifespan of 15–20 years were reported. The average duration of the blast crisis is4.5 months, with curbs of 0.5–15 months. Unless shifting into the acceleration phase, the quality of life of the patients is satisfactory, with maintenance of the working capacity. Early progression to acute phase remains the main cause of CML-related death. A number of emerging biomarkers with prognostic significance are currently under investigation, and early identification of patients who are at high risk of transformation should

become possible. A more challenging task is finding the effective therapies for identified high-risk patients and patients diagnosed in the acute phase. This may rely on the clinical development of small molecule inhibitors with novel mechanisms of action and synergistic activity against BCR-ABL1+ cells. Allogeneic HSCT, as well as TKIs may be considered as curative options for the recovery of patients with CML in the chronic phase [4, 7,8,14,18,19,21,22,23,24,41].Advances in allogeneic HSCT, such as the ongoing decrease in transplant-related mortality and improvements in supportive care, may be vitally important for high-risk patients and patients with acute phase of the disease.

Clinical case studies

Clinical case 1

A 70-year-old woman presents general weakness, discomfort and pain in the left upper abdominal quadrant, paleness of the face and night sweats. She has been considered ill for two years. She was treated for chronic hepatitis by a therapist.

Physical exam: Severe patient's condition. ECOG-WHO score 3. Pale skin. Impalpable peripheral lymph nodes. Lung exam: a vesicular murmur is determined. Heart sounds are rhythmical and quiet. Apical systolic murmur is detectable. Pulse rate is 92 beats/min. Blood pressure - 110/70 mm/Hg. The liver is palpable +3 cm below the costal margin. The spleen is palpable at the umbilical line.

Peripheral blood count: Hb – 98 g/l, RBCs – $3.2x10^{12}$/l, WBCs – $102.0x10^{9}$/l, reticulocytes –47‰, PLT – $511.0x10^{9}$/l, blast cells – 4%, promyelocytes – 6%, myelocytes – 30%, metamyelocytes – 4%, bands - 12%, segm. – 35%, eos. – 2%, bas. – 4%, lymph. – 1%, mon. – 2%, erythrocyte sedimentation rate – 24 mm/h.

Biochemical test: unconjugated bilirubin 25 mcmol/l, total bilirubin-29 mcmol/l, LDH 593 U/H, all other parameters are within the normal range.

Bone marrow aspiration: Hype rcellular. Myeloid cell line – 82%, with a shift to the left up to blast cells – 12%. Number of megakaryocytes is slightly increased. Erythroid cell lineage exhibits the signs of megaloblastichematopoiesis.

Abdominal ultrasound imaging: Splenomegaly: 26x12 cm, homogeneous structure. Hepatomegaly: RL 17 cm, LL 11 cm, diffuse changes.

1. What diagnosis would you establish?
2. Could you develop an investigation plan?
3. What treatment planissuitable for this case study?

Clinical case 2

A 52- year-old man complains of fatigue, periodical headache, left upper abdominal quadrant discomfort, paleness of the face. The patient has been considered ill for one year, with gradual occurrence of the above mentioned sings. His condition has worsened over the last 3 months.

Physical exam: ECOG-WHO score 2. Face, arms and upper torso are slightly pale. Lungs: a vesicular murmur is determined. Heart sounds are rhythmical and quiet. Pulse rate is 86 beats/min. Blood pressure-110/70 mm/Hg. The liver is palpable at the level of costal margin. The spleen is palpable +5 cm below the left costal margin.

Peripheral blood count: Hb – 110 g/l, RBCs – $3.8x10^{12}$/l, WBCs – $74.2x10^{9}$/l, reticulocytes –12‰, PLT – 456.0 $x10^{9}$/l, blast cells – 1%, promyelocytes – 2%, myelocytes – 4%, metamyelocytes – 7%, bands – 5%, segm. –56%, eos. – 2%, bas. – 1%, lymph. – 10%, mon. – 4%, erythrocyte sedimentation rate – 26 mm/h.

Biochemical test: LDH 481 U/H, all other parameters are within the normal limits.

Bone marrow aspiration: Hypercellular, myeloid cell line - 81%, with a shift to the left up to blast cells – 8%. Number of megakaryocytes is slightly increased.

Abdominal ultrasound imaging: Splenomegaly: 18.5x9 cm, homogeneous structure. Liver: RL 15.5 cm, LL 9 cm, diffuse changes.

1. What diagnosis would you establish?
2. Could you develop the plan of examination?
3. How would you perform the differential diagnosis?
4. Could you develop the treatment plan?

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Clinical case 3

A man, 41 years old, addressed with fatigue, left upper abdominal quadrant discomfort, paleness of the face. The patient has been considered ill for two years, with gradual occurrence of the above mentioned sings. His condition has worsened over the last 2 months.

Physical exam: ECOG-WHO score 3. Face, arms and upper torso are pale. Lungs: a vesicular murmur is determined. Heart sounds are rhythmical and quiet. Pulse rate is 92 beats/min. Blood pressure -110/70 mm/Hg. The liver is palpable +4 cm below the costal margin. The spleen is palpable +12 cm below the left costal margin.

Peripheral blood count: Hb – 91 g/l, RBCs– $3.1x10^{12}$/l, WBCs – $120.2x10^{9}$/l, reticulocytes – 31‰, PLT – $74.0x10^{9}$/l, blast cells – 8% myelocytes – 10%, metamyelocytes – 6%, bands – 5%, segm. – 43%, eos. – 2%, bas. – 1%, lymph. – 10%, mon. – 4%, erythrocyte sedimentation rate – 21 mm/h.

Biochemical test: LDH 754 U/H, uric acid –439 U/H, all other parameters are within the normal limits.

Bone marrow aspiration: Hypercellular. Myeloid cell line –90%, with a shift to the left up to blast cells – 21%. Number of mega-karyocytes is decreased.

The RT-QPCR reveals p210 transcript of the BCR-ABL chimeric gene – 100%.

Abdominal ultrasound imaging: Splenomegaly: 23.5x12 cm, homogeneous structure. Liver: RL 17.5 cm, LL 11 cm, diffuse changes.

1. What diagnosis would you determine?
2. Could you develop the investigation plan?
3. How would you perform the differential diagnosis?
4. Could you develop the treatment plan?

Control tests

S Chronic myeloid leukemia develops due to mutation at the level of:

A. Blast cell
B. Stem cell
C. Lymphoid B-cell precursor
D. Lymphoid T-cell precursor
E. Myeloid cell precursor
Correct answer: **B**

S In the early chronic phase of chronic myeloid leukemia, the leukocyte count is:

A. $> 30{,}0 \cdot 10^9$/l
B. $< 30{,}0 \cdot 10^9$/l
C. $> 60{,}0 \cdot 10^9$/l
D. $60{,}0 \cdot 10^9$/l
E. $100{,}0 \cdot 10^9$/l
Correct answer: **B**

S The most constant symptom of chronic myeloid leukemia is:

A. Lymph nodes enlargement
B. Hemorrhagic syndrome
C. Anemic syndrome
D. Splenomegaly
E. Involvement of pulmonary tissue
*Correct answer***: D**

S In chronic myeloid leukemia blood count shows leukocytosis in the account of:

A. Monocytes
B. Blast cells
C. Lymphocytes
D. Myeloid cells at all stages of maturation
E. Prolymphocytes
Correct answer: **D**

S The main clinical symptom of chronic myeloid leukemia and primary myelofibrosis is:

A. Central nervous system involvement
B. Splenomegaly
C. Lymph nodes enlargement
D. Bone pain
E. Involvement of pulmonary tissue
Correct answer: **B**

S The chronic phase of chronic myeloid leukemia is characterized by the following chromosome abnormality:

A. Translocation t(9;21)
B. Chromosome 9 deletion
C. Hypoploidy
D. Translocation t(15;17)
E. Translocation t(9;22)
Correct answer: **E**

S Which of the following features is characteristic of the onset of chronic myeloid leukemia:

A. Patient's satisfactory condition
B. Splenomegaly
C. Mediastinal lymph node enlargement
D. Leukocytosisupto $30{,}0 \cdot 10^9$/l
E. Shift to the left of the differential blood count up to myelocytes
Correct answer: **C**

S The most common clinical feature of chronic phase of chronic myeloid leukemia is:

A. Generalized lymph node enlargement
B. Hematodermia
C. Gingival hyperplasia
D. Splenomegaly
E. Vascular purpura
Correct answer: **D**

S In chronic phase of chronic myeloid leukemia, the first-line therapeutic option is:

A. Melphalan
B. Chlorambucil
C. Cytosine arabinoside
D. Cyclophosphamide
E. Imatinibmesylate
Correct answer: **E**

S In chronic myeloid leukemia a new chimeric gene is formed, namely:

A. TP53
B. BCR - ABL
C. CCND-1
D. BCL-2
E. BCL-6
Correct answer: **B**

S Choose the true statement regarding the spleen patterns in the early chronic phase of chronic myeloid leukemia:

A. The spleen extends 2-3 cm beyond the edge of the ribs
B. The spleen is not palpable
C. The spleen extends 4-5cm beyond the edge of the ribs
D. The spleen occupies half of the abdominal cavity
E. The spleen is impalpable at the umbilicus level
Correct answer: **B**

S The acute phase of chronic myeloid leukemia is confirmed by the presence of blast cells in the medullary puncture, the number of which may be:

A. > 10%
B. < 10%
C. > 25%
D. < 20%
E. > 15%
Correct answer: **C**

S Early chronic phase of chronic myeloid leukemia is characterized by:

A. Severe general condition;
B. Satisfactory general condition;
C. Fever not associated with infection;
D. Bone pains;
E. Anemia
Correct answer: **B**

S In chronic myeloid leukemia splenectomy may be carried out in case of:

A. Early chronic phase of the disease;
B. The phase of acceleration;
C. Frequent infarcts in the spleen;
D. DIC syndrome;
E. Acute phase of the disease
Correct answer: **C**

S In the acute phase of chronic myeloid leukaemia the clinical picture corresponds to the clinical picture of:

A. Chronic lymphocytic leukemia;
B. Acute leukemia;
C. Monocytic chronic leukemia;
D. Polycythemiavera;
E. Primary myelofibrosis
Correct answer: **B**

S Glivec (Imatinib mesylate) has the highest efficacy in the following phase of chronic myeloid leukemia:

A. Acute phase
B. Acceleration phase
C. Chronic phase
D. Acceleration and acute phases
E. In none of the mentioned phases
Correct answer: **C**

S In the Republic of Moldova, the morbidity of chronic myeloid leukemia per 100 000 inhabitants is as following:

A. 2.5
B. 0.9
C. 1.1
D. 0.6
E. 4.3
Correct answer: **D**

S From which of the following hematopoietic cells do leukemias develop?

A. Extramedullary proliferation of hematopoietic cells;
B. Hematopoietic cells of the bone marrow
C. Hematopoietic cells of the lymph nodes
D. Hematopoietic cells of the thymus
E. Blast hematopoietic cells
Correct answer: **B**

S Which of the following factors is important in the etiology of haematological malignancies?

A. Ionizing radiation
B. Aplastic crises in haemolytic anemias
C. Toxic agents from the group of aromatic hydrocarbons
D. Immune origin
E. Certain drugs (levomycetin, sulphanilamide, nonsteroidal anti-inflammatory drugs)
Correct answer: **A**

S Which of the following theories on the pathogenesis of haematological malignancies currently dominate:

A. The theory of " indigenous metaplasia "
B. The theory of clonal development of haematological malignancies
C. The mechanism of apoptosis in the oncogenesis of haematological malignancies

D. Tumor cells initially disseminated in the hematopoietic system

E. Most haematological malignancies cells have the capacity of dissemination and implantation up to their malignant transformation

Correct answer: **B**

S From which of the following cells do chronic leukemias develop?

A. Stem cells or precursor cells of hematopoiesis

B. Hematopoietic blast cells

C. Cells of granulocyte series

D. Cells of megakaryocyte series

E. Cells of erythrocyte series

Correct answer: **A**

S Which of the following must be taken into consideration in differentiating between acute and chronic leukemias:

A. Clinical course of leukemias

B. Morphological aspects of the cellular substrate

C. Hepatosplenomegaly

D. Gigantic splenomegaly

E. Generalized lymphadenopathy

Correct answer: **B**

S Which of the following hematologic malignancies develops from the stem cells of hematopoiesis?

A. Essential thrombocythemia

B. Acute leukemia

C. Chronic myeloid leukemia

D. Erythremia

E. Primary myelofibrosis

Correct answer: **C**

C In chronic myeloid leukemia the chimeric gene BCR-ABL produces the following changes in the activity of cells:

A. Decrease in the activity of mitogenic cells

B. Increase in the activity of mitogenic cells

C. Inhibition of apoptosis
D. Increased apoptosis
E. Reduced activity of tyrosine kinase
Correct answer: **B, C**

C In chronic myeloid leukemia infarcts in the spleen may be caused by:
A. Anemia
B. Thrombocytopenia
C. High leukocytosis
D. Leukopenia
E. Hypertrombocytosis
Correct answer: **C, E**

C Which of the following signs occurs in the accelerated phase of chronic myeloid leukaemia?
A. Lymphocytosis
B. Monocytosis
C. Non-infectious fever
D. Pain in the bones
E. Increase in general protein
Correct answer: **C, D**

C The following complications caused by hyperleukocytosis may develop in late chronic phase:
A. Anemia
B. Thrombocytopenia
C. Hemorrhagic syndrome
D. Splenic infarct
E. Thrombosis at the level of small vessels (retinal cavernous body)
Correct answer: **D, E**

C Bone marrow aspiration is performed in the following phases of chronic myeloid leukemia:
A. Early chronic phase
B. Late chronic phase

C. Accelerated phase
D. Acute phase
E. In all phases
Correct answer: **C, D**

C Early chronic phase of chronic myeloid leukemia is manifested by the following blood changes:

A. Leukocytosis> 30.0 x 10^9/l
B. Leukocytosis< 30.0 x 10^9/l
C. Leukopenia < 3.0 x 10^9/l
D. Shift to the left up to myelocytes
E. Lymphocytosis
Correct answer: **B, D**

C The following statements are true for the diagnosis of idiopathic myelofibrosis:

A. Absence of splenomegaly
B. Erythrocytes are normocytic
C. Anemia is uncommon
D. Thrombocytopenia is rarely observed
E. The platelet count is commonly increased
Correct answer: **D, E**

C In chronic myeloid leukemia, the bleeding syndrome results mainly from:

A. Decreased synthesis of coagulation factors
B. Thrombocytopenia due to the bone marrow failure
C. Functional disorders of platelets
D. Decreased fibrinolysin
E. Increased vascular fragility
Correct answer: **B, C**

C Which of the following drugs are commonly administered in the treatment of chronic myeloid leukemia:

A. Busulfan
B. Vinblastine
C. Prednisolone

D. Chlorambucil
E. Hydroxyurea
Correct answer: **A, E**

C Late chronic phase of chronic myeloid leukemia is characterized by:
A. Splenomegaly
B. Hemorrhagic syndrome
C. Shift to the left which correlates with leukocyte count
D. Complications caused by hyperleukocytosis (splenic infarction, edema of retina, thromboses of small vessels)
E. Lymph nodes enlargement
*Correct answer***: A, C, D**

C The following symptoms are characteristic for accelerated phase of chronic myeloid leukemia:
A. Erythrocytosis
B. Decreased efficiency of the performed cytotoxic treatment
C. Fever without evidence of infection
D. Bone pain
E. Decrease of spleen size
Correct answer: **B, C, D**

C Splenectomy may be performed in some cases of chronic myeloid leukemia, including:
A. Initial phase of the disease
B. Blast crisis
C. Frequent splenic infarctions
D. Thrombocytopenia
E. Marked abdominal discomfort
Correct answer: **C, D, E**

C In idiopathic myelofibrosis histological examination of the bone marrow reveals:
A. Polymorphous hypercellularity
B. Hypercellularity with domination of fibrosis
C. Marked increase of megacaryocytecount

D. Replacement of hematopoietic tissue by adipose cells
E. Diffuse infiltration by lymphoid cells
Correct answer: **A, B, C**

C The following complications may occur within the evolution of chronic myeloid leukemia:
A. Hyperuricemia
B. Splenic infarction
C. Autoimmune hemolyticanemia
D. Hepatic failure
E. Priapism
*Correct answer***: A, B, E**

C Which of the following statements are not true for the diagnosis of chronic myeloid leukemia:
A. Presence of splenomegaly
B. Presence of leukocytosis with shift to the left
C. Administration of chlorambucil for the treatment
D. Absence of chronic myeloid leukemia in children
E. Favorable prognosis
*Correct answer:***C, D, E**

C The following statements about chronic myeloid leukemia are true:
A. There is a correlation between the leukocyte count and spleen size
B. There is no correlation between the leukocyte count and spleen size
C. Erythrocytes are normocytic
D. Neutrophil alcaline phosphatase is decreased
E. Cytogenetic examination of the bone marrow cells is positive for Ph chromosome
Correct answer: **A,C,D,E**

C The following statements are true for the diagnosis of idiopathic myelofibrosis:

A. Marked shift to the left of the leukocyte count, with high percentage of myelocytes and metamyelocytes
B. Morphological examination of erythrocytes reveals marked anisocytosis and poikilocytosis
C. Neutrophil alcaline phosphatase is normal or increased
D. Anemia is common
E. There is no correlation between leukocyte count and spleen size
Correct answer: **B,C,D,E**

C The following clinical syndromes occur in the acute phase of chronic myeloid leukemia:

A. Anemic syndrome
B. Hemorrhagic syndrome
C. Infectious complications
D. Prolipherativesyndrome
E. Protein pathology
Correct answer: **A,B,C,D**

C The advanced stage of chronic monocytic leukemia is manifested by:

A. Anemic syndrome
B. Splenomegaly
C. Lymph nodes enlargement and hepatomegaly rarely
D. Lymphocytosis in the peripheral blood count
E. Monocytosis in the peripheral blood count
Correct answer: **A, B, C, E**

C Acute phase of chronic myeloid leukemia is characterized by:

A. Blast crisis
B. Transformation into acute myeloblastic leukemia
C. Sarcomatous growth
D. Transformation into acute lymphoblastic leukemia
E. Complete recovery
Correct answer: **A, B, C, D**

C Acute phase of chronic myeloid leukemia is characterized by:

- **A.** Resistance to chemotherapy with Busulphan
- **B.** Splenomegaly
- **C.** Bone pain
- **D.** Accelerated positive response to increased dosage of Busulphan
- **E.** Increased blast cells count in the peripheral blood

Correct answer: **A, B, C, E**

C In chronic myeloid leukemia, the chimeric gene BCR-ABL produces the following changes in the cell activity:

- **A.** It decreases the activity of mitogenic cells
- **B.** It increases the activity of mitogenic cells
- **C.** Impairment of cell adhesion to stroma
- **D.** Inhibition of apoptosis
- **E.** Intensification of apoptosis

Correct answer: **B, C, D**

C In the acute phase of chronic myeloid leukemia, the following syndromes can be observed:

- **A.** Anemic syndrome
- **B.** Paraproteinemic syndrome
- **C.** DIC syndrome
- **D.** Hemorrhagic syndrome
- **E.** Syndrome of infectious complications

Correct answer: **A, D, E**

C In chronic phase of advanced chronic myeloid leukemia the following complications caused by hyperleukocytosis may develop:

- **A.** Hemorrhagic syndrome
- **B.** Splenic infarct
- **C.** Retinal edema
- **D.** Stupor
- **E.** Thrombosis in the small vessels (retinal cavernous body)

Correct answer: **B, C, D, E**

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