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CLINICAL CASE OF TREATMENT OF A PATIENT WITH CHRONIC MYELOID LEUKEMIA WITH A MUTATION *BCR-ABL* Y253H AND COMORBIDITIES

Abstract

The article presents information on the methods of diagnosis and targeted therapy of chronic myeloid leukemia (CML). A clinical case of CML with the development of resistance to therapy with 1st generation tyrosine kinase inhibitors (ITK), the appointment of 2nd generation ITK (dasatinib) with regard to comorbidity, the development of adverse events in the form of fibrosing alveolitis and severe pleurisy, translation of nilotitis in the form of fibrosis of the alveolitis and severe pleurisy is considered, but the lack of effect of treatment. The study of the mutational status revealed a *BCR-ABL* Y253H mutation, which made it possible to individualize the patient's therapy, obtain a large molecular response, and overcome undesirable phenomena. The development of resistance or the loss of response to the treatment of ITK in CML with comorbidity requires the timely identification of mutations in the kinase domain of *BCR-ABL* and contributes to the selection of early personalized therapy for a particular patient.

Key words: *clinical case, chronic myeloid leukemia, tyrosine kinase inhibitors, resistance, BCR-ABL mutation*

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BC — blast crisis, MMR — Major Molecular Response, TKI — tyrosine kinase inhibitors, CHR — Complete Hematologic Response, CCyR — Complete Cytogenetic Response, APh — accelerated phase, CML — chronic myeloid leukemia, CPh — chronic phase

Introduction

Chronic myeloid leukemia (CML) is a chronic disease of blood and bone marrow, a clonal myeloproliferative process that develops as a result of malignant transformation in early hematopoietic progenitor cells [14].

The incidence is approximately 1:100.000 of the population. Peak incidence occurs between the ages of 30–50 years, and about 30 % of the patients are older than 60 years [3, 13].

The unique feature of CML is the presence of a specific marker in tumor cells: t (9;22) (q34;q11) translocation, known as the Philadelphia chromosome (Ph-chromosome) and, respectively, chimeric oncogene *BCR-ABL*. The production of *BCR-ABL*-dependent tyrosine kinase (P210 protein) plays a key role in leukemic cell transformation in CML [1, 3, 9].

Presence of CML can be assumed on the basis of the following clinical and complete blood count data: leukocytosis, myeloid shift, basophilia and

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eosinophilia, anemia, thrombocytosis or thrombocytopenia, hepato-and splenomegaly. Detection of Ph chromosome by cytogenetic method or *BCR-ABL* gene by molecular genetic method is mandatory for diagnosis of CML [14].

Three phases, which reflect the degree of disease progression, are distinguished in the clinical course of CML: chronic phase (CPh), accelerated phase (APh), blast transformation phase or blast crisis (BC). The disease can be newly diagnosed at any stage of the clinical course.

The aim of the modern therapy of CML is the maximal suppression of the Ph-positive tumor clone and the achievement of remission. The modern standard of treatment is therapy with *BCR-ABL* tyrosine kinase inhibitors (TKI). These medicines have a mechanism of targeted effect on *BCR-ABL*-positive tumor cells. This reduces the risk of disease progression and increases patient survival [1, 3, 8, 18]. CML treatment regimens have a clear procedure and are divided into first, second and third lines [2]. The remission of CML is determined by the following concepts: Complete Hematologic Response (CHR) — the number of blood cells is within the normal range and studies do not reveal immature forms of leukocytes. Spleen size is reduced to the normal. Complete Cytogenetic Response (CCyR) — no cells with Philadelphia chromosome (*BCR-ABL*) are revealed by bone marrow cytogenetics. Major Molecular Response (MMR) — PCR test still reveals *BCR-ABL*, however, at a low level (less than 0.1 %). Such response is considered optimal among experts. Complete Molecular Response (CMR) — PCR test still reveals *BCR-ABL*, however, at a very low level up to the technical detection limit (the level is lower than 0.01 % at MR4 and lower than 0.0032 % at MR4.5). Molecularly Undetectable Disease — PCR test does not reveal *BCR-ABL* in the blood or bone marrow [5, 15]. However, most patients may still have a very small number of copies of the *BCR-ABL* gene that are not technically detectable.

Mutational analysis of *BCR-ABL* is carried out in the acceleration phase and in the blast crisis. Also, the presence of the *BCR-ABL* tyrosine kinase domain mutations is recommended to be studied in case of treatment failure and before TKI switching [12, 16, 19]. Mutation in the *BCR-ABL* gene in particular is a common cause of the formation of resistance to TKI therapy, which is found in approximately 16–20 % of patients [4, 6, 7, 21].

A clinical case of a patient with chronic myeloid leukemia, resistance to target therapy with tyrosine kinase preparations and having the *BCR-ABL* mutation Y253H is presented. According to the literature, this mutation occurs in CML in 6–10 % of all cases of the *BCR-ABL* kinase domain mutations and is characterized by the most unfavorable prognosis and short survival, even worse than with the T315I mutation [17].

Case Report

Patient F., 64 years old, was first admitted to the Hematology Department in November 2011 for examination and treatment with the following preliminary diagnosis: Chronic myeloid leukemia, chronic phase. Upon admittance complained of aching pain in the left upper quadrant while in the left side position, fatigue, sweating, fever up to 37 °C, headache. Felt sick for a month. The examination at the local health facilities revealed changes in the complete blood count — leukocytosis, thrombocytosis; ultrasound scanning revealed splenomegaly (+5 cm). To clarify the diagnosis, the patient was referred to a hematologist for consultation. Past medical history includes childhood infections, ARVI, tonsillitis, surgical treatment for purulent process in the coccyx area in 1986. Coronary heart disease, postinfarction (2002) cardiosclerosis. Allergic and family history are not compromised. No bad habits. Physical examination results: state of moderate severity, clear consciousness, active position, skin is pink, clean, moist, subcutaneous tissue of moderate development, body temperature is 37.2 °C. No swelling is detected. Lymph nodes are not palpable. Vesicular breathing over the lungs, no crackles. Respiratory rate is 17 breaths per minute Heart sounds are muffled, regular. BP 145/90 mm Hg, HR — 72 bpm. Digestive organs: tongue is moderately white. Abdomen is soft, moderately painful in the left upper quadrant. Liver is +2 cm from the costal margin, spleen is +4–5 cm from the costal margin. Ultrasound scanning: enlarged spleen, dimensions: 186×76×102 mm, enlarged liver +10 cm, left kidney cyst, diffuse changes of pancreas.

Complete blood count (CBC) reveals leukocytosis, thrombocytosis, leukocyte left shift to poorly differentiated forms of neutrophils: erythrocytes — 4.10×10^{12}/l, hemoglobin — 115 g/l, mean corpuscular volume — 87, platelets — 1277×10^{9}/l, leukocytes — 137×10^{9}/l, blasts — 2 %, promyelocytes — 4 %, myelocytes — 17 %, monocytes — 3 %, lymphocytes — 8 %, segmented neutrophils — 52 %, stab cells — 2 %, immature neutrophils — 2 %, basophils — 10 %. Bone marrow cell differential count: myelocaryocytes — 255,000, megakaryocytes — 210, myeloblasts — 13.0 %, promyelocytes — 1.0 %, myelocytes — 19 %, metamyelocytes — 4 %, stab cells — 12.7 %, segmented neu. — 26.0 %, e — 11 %, l — 1 %, m — 3 %, normoblasts — 9 %. Conclusion: bone marrow is hypercellular, polymorphic. Irritated megakaryocyte lineage. Minor irritation of myeloid lineage. Increased number of blast cells. Increased eosinophil count to eosinophilic myelocytes. Erythroid lineage is narrowed. Specific translocation t (9; 22) (q34; q11), so-called Philadelphia chromosome (Ph-chromosome), was discovered in 100 % of metaphases by cytogenetic study.

Based on clinical, laboratory data and cytogenetic studies, according to WHO and ELN criteria, a clinical diagnosis was established: *Principal:* Chronic myeloid leukemia, chronic phase. *Secondary:* Coronary artery disease. Postinfarction cardiosclerosis (2002). Hypertension stage II, grade 3, risk 4 (according to the Russian Hypertension Classification).

To manage leukocytosis and thrombocytosis the patient received therapy with hydroxycarbamide (Hydrea) at a dose of 2000 mg/day. To prevent complications associated with tumor lysis syndrome in the cytoreduction period, the patient took allopurinol 300 mg/day, combined with copious hydration regimen. From the end of December 2011, the patient started taking 1st line tyrosine kinase inhibitors (TKI) with imatinib (Gleevec) 400 mg/day on an outpatient basis with a positive effect. From June 2012, the deterioration of hematological parameters occurs: leukocytosis — 16.5×10^{9}/l, thrombocytosis — 1863×10^{9}/l. The absence of Hematological and Cytogenetic Response was an indication for increasing the dosage of imatinib (Philachromin) to 600 mg per day.

In July 2012, the deterioration of general well-being, the appearance of severe shortness of breath during exercise developed. An additional examination was carried out, the patient was consulted by a cardiologist, pulmonologist; a diagnosis was established: Interstitial lung disease. Fibrosing alveolitis. Respiratory failure II. Emphysema. Therapy with prednisolone 30 mg per day was prescribed with a gradual decrease of the dose, verospiron 25 mg in the morning constantly. The patient felt satisfactory.

In October 2012, a change in the complete blood count, an increase in platelet level to 3500×10^{9}/l was detected again. Reaferon 3 MIU intramuscularly every other day, hydroxycarbamide (Hydrea) 2000 mg per day were added to the TKI treatment, however, normalization of CBC was not achieved.

In June 2013, the patient was admitted to the Hematology Department due to increasing fatigue, dyspnea, absence of Hematological and Cytogenetic Responses. Leukocytosis, thrombocytosis, left leukocyte shift were still present in CBC: ESR — 39 mm/hour, leukocytes — 39×10^{9}/l, erythrocytes — 3.62×10^{12}/l, hemoglobin — 134 g/l, platelets — 1488×10^{9}/l, blasts — 2 %, promyelocytes — 4 %, myelocytes — 21 %, immature — 5 %, stab — 9 %, segmented — 39 %, eosinophils — 3, monocytes — 55 %, basophils — 18 %, lymphocytes — 8 %, normoblasts — 1:100. As a result of the 1st line therapy failure, the patient was switched to the 2nd line of TKI therapy. When choosing medication, the concomitant diseases of the patient were taken into account: as he suffered myocardial infarction in 2002 and has a high risk of cardiovascular complications, dasatinib therapy (Sprycel) was started at a dosage of 100 mg per day. The therapy was tolerated satisfactorily. During the treatment, Complete Hematological Response was achieved within a month. On 02.10.2013, a molecular genetic study to determine the expression of the *BCR-ABL* gene returned a negative result, which indicates the achievement of Complete Molecular Response.

However, in December 2013 a marked deterioration of health, aggravated dyspnea, cough with mucoid sputum, fever were observed. In January 2014, the patient was again admitted to the Hematology Department in a severe condition. According to the results of the examination, a diagnosis

was established: Bilateral hydrothorax. Respiratory failure II (Fig. 1).

Fluid retention (pleural and pericardial effusions, pulmonary edema) is one of the frequent adverse effects of dasatinib (Sprycel) treatment. In this regard, the patient was switched to nilotinib (Tasigna) 400 mg 2 times a day. The medication was tolerated well, the condition was satisfactory. CBC: ESR — 9 mm/hour, leukocytes — 5.6×10^{9}/l, erythrocytes — 5.0×10^{12}/l, hemoglobin — 138 g/l, platelets — 206×10^{9}/l. Molecular genetic study on

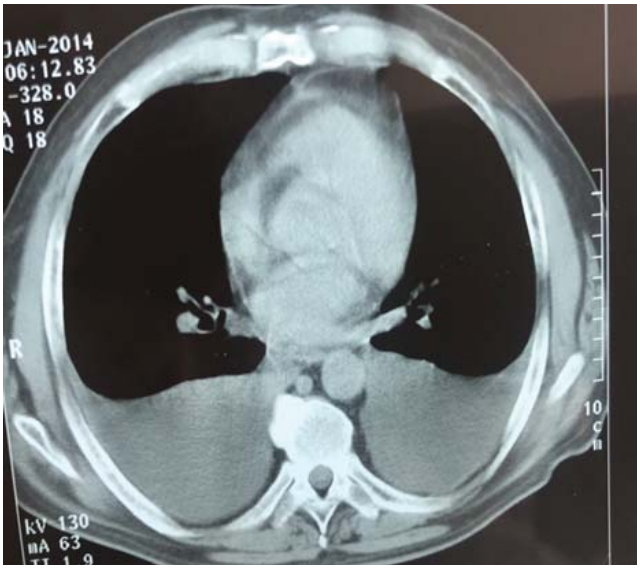

Figure 1. *Bilateral hydrothorax. One of a series of images of a computerized tomography of the chest from January 6, 2014*

22.10.2014 showed that the expression of the *BCR-ABL* gene is 0.13 %. Response to therapy: Complete Hematological Response and Major Molecular Response were achieved.

In August 2015, after suffering moderately severe acute respiratory viral infection, deterioration of blood count was observed. Leukocytosis and thrombocytosis were observed in CBC: leukocytes — 19.0×10^{9}/l, platelets — 1180×10^{9}/l. The treatment was supplemented with Reaferon at a dose of 3 MIU every other day, the effect was insignificant. Cytogenetic study: Ph-chromosome in 100 % of metaphases. Molecular genetic study: expression of the *BCR-ABL* gene — 10.04 %. The therapy was continued.

In November 2016, cytogenetic and molecular studies showed negative changes. A molecular genetic study on 10.11.2016 showed that the expression of the *BCR-ABL* gene was 53.3 %. Due to the failure of therapy, analysis of mutations of the *BCR-ABL* kinase domain was performed, and the Y253H mutation with resistance to imatinib, nilotinib, moderate resistance to dasatinib, sensitivity to bosutinib (Table 1) was detected.

Due to the progressive course of the disease, presence of bosutinib-sensitive mutation, development of pleurisy earlier during dasatinib therapy (Sprycel), the patient was consulted in the FBHI „V.A. Almazov NMRC" of the Ministry of Health of the Russian Federation. Principal Diagnosis:

Table 1. *Dynamics of drug administration and patient treatment results*

Medicine	Period of Therapy	Hematologic Response	Cytogenetic Response	Molecular Response	Adverse Effects, Complications
Imatinib 400 mg/day	From December 2011	PHR	No	No	Edema
Imatinib 600 mg/day + Reaferon	From June 2012	No	No	No	Interstitial pneumonia — July 2012
Dasatinib 100 mg/day	From June 2013	CHR	CHCyR	CMR (2.10.13)	bilateral hydrothorax, Respiratory failure II — December 2013
Nilotinib 400 mg/day	From January 2014	CHR	CHCyR	MMR — 0.13 % (22.10.14)	No
+ Reaferon 3 MIU 3 times/ week	From August 2015	Loss of HR after ARVI	Loss — 100 %	Loss of MR — 10 %, further 53 % (November 2016)	Y253H mutation detected
Dasatinib 100 mg/day	From January 2017 till present	CHR	MCyHR	MMR — May 2017	Dyspnea, cough

Chronic myeloid leukemia, accelerated phase. Cytogenetic resistance and 3rd-4th grade intolerance on the background of therapy with imatinib. Y253H mutation. Secondary: CHD Postinfarction cardiosclerosis (2002). Hypertension stage II, grade 3, risk 4 (according to the Russian Hypertension Classification). Fibrosing alveolitis. Emphysema. Pneumosclerosis. Respiratory failure I, non-acute. Recommended treatment according to vital indications preferably with bosutinib or dasatinib.

From January 2017 till present, the patient receives treatment with dasatinib (Sprycel). The condition is satisfactory. CBC from May 2018: ESR — 17 mm/hour, leukocytes — 4.2×10^9/l hemoglobin — 116 g/l, platelets — 116×10^9/l. Complete Hematological Response, Complete Cytogenetic Response and Major Molecular Response are achieved. There are no serious AEs.

Discussion

The patient was diagnosed with chronic myeloid leukemia based on clinical and laboratory data and cytogenetic study with detection of the pH-chromosome, according to WHO and ELN criteria. Currently, the main way of therapy and standard of treatment is therapy with the inhibitor of *BCR-ABL* tyrosine kinase (TKI) [1, 2]. These medicines have a mechanism of targeted effects on *BCR-ABL*-positive tumor cells and should be prescribed to all newly diagnosed patients [3, 13]. To achieve the goal of modern treatment of CML — the maximum suppression of Ph-positive tumor clone, as the first line of therapy, TKI of the 1st generation imatinib (Gleevec) 400 mg/day was selected. Because of absence of Cytogenetic Response and hematological remission, the dose of imatinib was increased to 600 mg per day. Despite the increase in the dose, no significant effect of treatment was obtained. This was an indication for a shift to the 2nd line TKI therapy. Dasatinib therapy was started (Sprycel) at a dose of 100 mg per day. Complete Hematological and Molecular Response was achieved during the treatment. However, therapy was complicated by the manifestation of non-hematological toxicity of the medicine in the form of fluid accumulation in body cavities with the development of severe pleurisy [4, 11]. The mere fact of the appearance of pleural effusion on the background of dasatinib therapy does not worsen the prognosis, but reduces adherence to the treatment, disrupting the continuity of the therapy. It was decided to change the medication to nilotinib (Tasigna) at a dosage of 400 mg 2 times a day. Response to therapy: Complete Hematological Response, Complete Cytogenetic Response, Major Molecular Response. After acute respiratory viral infection, a deterioration of blood parameters occurred. A loss of Cytogenetic and Molecular Responses was noted. When ascertaining treatment failure, *BCR-ABL* mutation analysis is advisable. [10]. Mutations cause low sensitivity and full resistance to TKI therapy. The patient was found to have the Y253H mutation with resistance to imatinib, nilotinib, moderate resistance to dasatinib, sensitivity to bosutinib. The literature describes mutations that cause low sensitivity of nilotinib therapy: Y253H, E255K/V, F359V/C. When these mutations are detected, dasatinib therapy is preferable [3, 7]. According to S. Severini (2016), the Y253H mutation is more common with relapses of the second line therapy with nilotinib [20].

Considering the presence of the Y253H mutation, concomitant diseases, the clinical course of disease, and the patient's adherence to treatment with dasatinib, regular therapy with II-generation TKI — dasatinib (Sprycel) 100 mg per day was continued. The medication was tolerated satisfactorily, no adverse effects recurred. To assess the condition, monitoring of the treatment and results is carried out. In the course of therapy, Complete Hematological, Cytogenetic and Major Molecular Responses were obtained, which indicates the correct tactics of management of the patient.

Conclusion

The development of resistance or loss of response to TKI treatment in chronic myeloid leukemia with comorbidity requires timely identification of mutations in the *BCR-ABL* kinase domain and contributes to the selection of early personalized therapy for a particular patient.

Conflict of interests

The authors state that this work, its theme, subject, and content do not affect competing interests

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