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CASE REPORT

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Ponatinib in treatment of chronic myeloid leukemia with *T315I* mutation

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Abstract

Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm associated with a characteristic chromosomal translocation t(9;22)(q34;q11) which causes the formation of the Philadelphia chromosome (Ph). Therapeutic progress made in the last two decades and new-generation tyrosine kinase inhibitors (TKIs) introduction, signifi cantly increased patients' prognosis. We present a case study of a Ph-positive CML patient with a point BCR/ABL1 mutation T315I treated with ponatinib.

Key words: chronic myeloid leukemia, CML, Philadelphia chromosome, *T315I* mutation, TKIs, ponatinib

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Introduction

Chronic myeloid leukaemia (CML) is a neoplastic disease classified as myeloproliferative neoplasm, the pathomechanism of which is associated with the presence of the translocation t (9; 22)(q34; q11). The result of this aberration is a formation of truncated chromosome 22 referred to as the Philadelphia chromosome (Ph). The translocation results in the Abelson gene (Abl1) on chromosome 9 coming together with the *BCR* gene located on chromosome 22. This leads to constitutive production of BCR-ABL1 protein which has tyrosine kinase activity and promoting the proliferation of granulocytic lineage cells. Neoplastic cells with *BCR-ABL1* fusion gene are genetically unstable, which can lead to the different clinical presentation of the disease including chronic phase, acceleration phase and the most aggressive blast phase. Progression and resistance to treatment may be determined by the appearance of additional mutations in the *BCR-ABL1* gene. *T315I* mutation determines treatment resistance to all medications of the first- and second-generation group of tyrosine kinase inhibitors (TKI) [1].

Thanks to therapeutic advances made in the last two decades and new TKIs, most of the patients being in the chronic phase achieve life expectancy close to the healthy population. It also becomes possible to consider discontinuation of so far lifelong therapy after achieving a stable deep molecular response and sustaining treatment-free remission (TFR). In case of disease progression or failure to achieve an optimal therapeutic response, it is important to define the presence of point mutations in the BCR-ABL1 kinase domain (KD BCR-ABL1) which may cause resistance to treatment. Ponatinib belongs to the group of TKIs and is effective against all clinically significant KD BCR-ABL1 mutations. This drug can be used in the third line treatment of CML or resistance to the second-generation TKIs and any treatment line in patients with identified *T315I* mutation [2].

Case report

This study presents a case of a patient diagnosed with Ph+ CML and treated sequentially with subsequent TKIs (imatinib, nilotinib, ponatinib) belonging to all three generations of this group of drugs.

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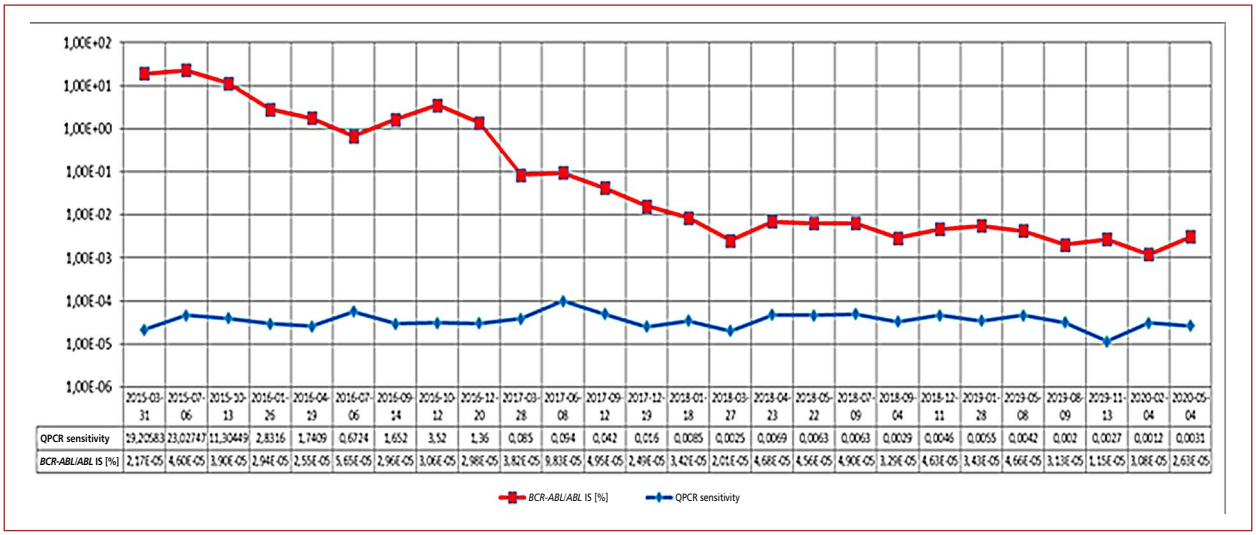
A 64-year-old patient with a history of psoriasis was admitted to the Haematology Department of University Teaching Hospital in Bialystok in December 2014 due to a suspected neoplastic process of bone marrow. Subjectively, the patient was not reporting haematologically significant complaints/symptoms, the general condition of the patient was good, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale was 0. On physical examination, there was splenomegaly with spleen palpable 2 cm below the costal margin. Laboratory results showed leukocytosis (80.15 G/L) with a left shift in granulocytic lineage, anaemia of mild degree [hematology (Hb) 11 g/dL] and thrombocytosis (687 G/L). The material obtained during bone marrow biopsy was sent to cytogenetics laboratory to proceed with cytogenetic testing with classic method (GTG, G--bands by trypsin using Giemsa) and fluorescent *in situ* hybridization (FISH). In the analysed material, in all metaphases (22 metaphases were analysed) the presence of translocation between five chromosomes was found the result of which was the Philadelphia chromosome — der(22) — and other 4 derived chromosomes:

- der(5), composed of the long arm of chromosome pair 22 and the chromosome of 5th pair from region 5p13 to 5qter;
- der(8), composed of chromosome pair 8 (from 8pter to 8q24), the long arm of the 9th chromosome pair (from 9p13 to 9q34) and the long arm of the 10th chromosome pair (from 10q21 to 10qter);
- der(9), composed as deletion of the long arm of chromosome pair from region 9q13;
- der(10), composed of chromosome pair 10 (from pter to 10q21) and the short arm of chromosome pair 5 (from 5p13 to 15pter);

The above aberrations were confirmed by the FISH technique with the use of painting probes for the chromosomes of pair 8, 9, 20 and 22. The study was performed with a resolution of about 400 fringes per haploid set of chromosomes. Molecular testing by the real-time quantitative polymerase chain reaction (RQ-PCR) method demonstrated the presence of *BCR-ABL* p210 transcript (transcript type b3a2). CML in the chronic phase was diagnosed.

Due to significant leukocytosis, while awaiting cytogenetic and molecular test results, the patient was given cytoreductive therapy with hydroxycarbamide 2 g per day, then treatment with imatinib (Glivec, Novartis) 400 mg per day was introduced from 8th January 2015. The treatment with TKI was well tolerated by the patient. During subsequent follow-up tests, gradual improvement of FBC parameters was observed achieving their normalization after 3 months of imatinib therapy. The results of cytogenetic testing performed 11 months after diagnosis showed the presence of a Ph chromosome in 90% of metaphases. The patient qualified for treatment with nilotinib (Tasigna, Novartis) 400 mg twice a day, which he was receiving from 3rd November 2015. The initial period of nilotinib treatment was complicated by an allergic skin reaction in the form of pruritus and skin redness and hypertension at night-time to the value of 210/ /100 mm Hg. Nilotinib treatment was discontinued for approximately 2 weeks. After drug reintroduction, skin reaction or high blood pressure were no longer observed. Laboratory studies showed three-lineage cytopenia not requiring medical intervention and increased bilirubin levels — side effects did not exceed grade 2 according to the Common Toxicity Criteria (CTC). *BCR-ABL1* transcript assessment by RQ-PCR performed in the 3rd month during second-line treatment showed a decrease in the amount of *BCR-ABL1* transcript (2.8% IS; Figure 1). After one year of treatment with a standard dose of nilotinib the patient did not achieve a major molecular response (MMR) — therefore tests were performed for the presence of *BCR/ABL1* mutations. *T315I* point mutation was proven. Nilotinib therapy was discontinued and treatment with ponatinib (Iclusig, Incyte) 45 mg per day was commenced from 2nd January 2017. During the initial period of the therapy, laboratory tests showed increased lipase levels (grade 1 according to CTC). Blood count parameters were within the reference range. Due to diagnosed psoriatic arthritis, treatment with methotrexate was introduced resulting in a reduction of joint symptoms, which did not have any effect on developing any haematological or non-haematological treatment toxicities. After approximately 3 months of treatment with ponatinib, MMR was achieved. One year after initiation of treatment with the third-generation inhibitor, the transcript value was 0.0085% [molecular response (MR) 4.0]. TKI dose was reduced to 30 mg per day. In September 2018, MR 4.5 was reached, after the next three months — MR 4.0. Molecular response at 4.5 level was achieved again in August 2019. The patient's assessment — history and physical examination — carried out in June 2020 showed no significant haematological abnormalities, ponatinib is well--tolerated, molecular response MR 4.5 is sustained by the RQ-PCR study (Figure 1). The patient continues treatment with TKI.



	2015-03-31	2015-07-06	2015-10-13	2016-01-26	2016-04-19	2016-07-06	2016-09-14	2016-10-12	2016-12-20	2017-03-28	2017-06-08	2017-09-12	2017-12-19	2018-01-18	2018-03-27	2018-04-23	2018-05-22	2018-07-09	2018-09-04	2018-12-11	2019-01-28	2019-05-08	2019-08-09	2019-11-13	2020-02-04	2020-05-04
QPCR sensitivity	19,20583	23,02747	11,30449	2,8316	1,7409	0,6724	1,652	3,52	1,36	0,085	0,094	0,042	0,016	0,0085	0,0025	0,0069	0,0063	0,0063	0,0029	0,0046	0,0055	0,0042	0,002	0,0027	0,0012	0,0031
BCR-ABL/ABL IS [%]	2,17E-05	4,60E-05	3,90E-05	2,94E-05	2,55E-05	5,65E-05	2,96E-05	3,00E-05	2,98E-05	3,82E-05	9,83E-05	4,95E-05	2,49E-05	3,42E-05	2,01E-05	4,68E-05	4,56E-05	4,90E-05	3,29E-05	4,63E-05	3,43E-05	4,66E-05	3,13E-05	1,15E-05	3,08E-05	2,63E-05

Figure 1. Molecular results of the real-time quantitative polymerase chain reaction (RQ-PCR) method for the presence of the *BCR-ABL* p210 transcript; the referen *ABL* gene; the arrows indicate the time of starting particular lines of therapy with tyrosine kinase inhibitors

Discussion

The use of TKIs in patients with CML has led to significant treatment progress in this group of patients. The presented case is an example of the use of three generations of drugs from the TKI group, but only ponatinib allowed to obtain deep molecular response (DMR) giving a chance for long-term disease control.

Achieving MMR early can translate to better treatment outcomes for patients [3], therefore testing of the presented patient for *BCR-ABL1* gene mutation before switching to second-generation TKI could have contributed to an earlier choice of ponatinib as an effective drug showing antileukemic activity and the only effective inhibitor in patients with the presence of *T315I* mutation [4].

Treatment with ponatinib may be associated with the occurrence of side effects, including pancreatitis among others [5]. During a period of over 3-year treatment with ponatinib, the patient has not experienced any clinically significant complications of TKI therapy requiring treatment modifications. The use of methotrexate for psoriatic arthritis during treatment with ponatinib did not cause drug toxicities either. In conclusion, as recommended by the European LeukaemiaNet in 2020 ponatinib is the only drug in the group of available TKIs and demonstrates clinical activity when *T315I* mutation is found therefore it is recommended in any line of treatment whenever such mutation is confirmed.

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