VIA MEDICA

CLINICAL VIGNETTE

Acta Haematologica Polonica 2023
Number 4, Volume 54, pages 263–265
DOI: 10.5603/AHP.a2023.0045
ISSN 0001–5814
e-ISSN 2300–7117

Secondary resistance to imatinib in child with chronic myeloid leukemia as result of mutations in BCR-ABL1 kinase domain

Katarzyna Martyna Pawelec*, Katarzyna Albrecht

Department of Pediatric Hematology and Oncology and Clinical Transplantology, Medical University of Warsaw, Poland

Chronic myeloid leukemia (CML) rarely occurs in the first few decades of life, accounting for 2–3% of leukemias in children [1–3]. CML is a myeloproliferative neoplasm that results from translocation t(9:22) and the resultant *BCR-ABL1* fusion. Most patients (80%) are diagnosed with CML during the initial chronic phase (CP). Current therapeutic approaches for CML-CP aim to decrease leukemic cell numbers and prevent disease progression by inhibiting *BCR-ABL1* kinase activity. Imatinib (IM) treatment of CML is very effective and has become the standard of care in the chronic phase (CP) [4, 5]. However, *ABL1* kinase mutations occur in the course of CML regardless of the treatment with tyrosine kinase inhibitors (TKIs), and in many cases they are responsible for the development of primary and secondary resistance to drugs from this group. Obtaining a suboptimal response, lack of response to treatment, or its loss, are all indications for their presence.

Dasatinib is an effective treatment for the majority of patients with CML-CP who have developed an imatinib-resistant *BCR-ABL1* mutation, and is associated with durable responses and favorable long-term outcomes [6–8].

An 11-year-old girl, previously healthy, was admitted to the clinic due to abnormal results of a blood count performed before a sports competition. Her general condition was good. She had a heart murmur, a large spleen extending to 25 cm below the costal margin, and an enlarged liver 3.5 cm. Blood tests showed hyperleukocytosis: white blood cell count: 254.51 × 10^3/μL, anemia: red blood cell (RBC) count 2.81 × 10^6/μL, hemoglobin (Hb) 7.1 g/dL and thrombocythemia: platelets (PLT) 861 × 10^3/μL. The result of a bone marrow aspirate and biopsy was consistent with CML in the chronic phase (CML-CP). She was started on imatinib 300 mg/m^2 orally once daily. Her blood counts normalized within a month, but the splenomegaly persisted (+17 cm) and reached normalization during the following month.

However, *BCR-ABL1* transcript level by real-time quantitative polymerase chain reaction (RQ-PCR) assay at three months was 13.1% and at five months was 1.91% [on the International Scale (IS)] (Figure 1). She tolerated the imatinib treatment without significant toxicity. Her parents confirmed that she was taking imatinib daily without missing any doses. Mutational analysis showed kinase domain (KD) *BCR-ABL1* mutations pathogenic variant: G250E. This variant is sensitive to dasatinib with resistance to imatinib, nilotinib and bosutinib. Switching to dasatinib therapy 100 mg/m^2/daily resulted in a major molecular response (MMR ≤0.1% IS) within three months. In the third year of MMR maintenance, a significant increase in the *BCR-ABL 1* transcript to 2.17% IS was found, which was confirmed by a study performed after two months of 6.34% IS.

Suspecting another resistance to treatment, human leukocyte antigen (HLA) matching tests were performed, considering hematopoietic cell transplantation as another therapy (no family donor). In addition, an interview was conducted with the now 15-year-old patient. It turned out that she had voluntarily discontinued the medication. After a break of almost five months, desatinib was resumed, and MMR was obtained again after nine months (Figure 1). Now the girl has an MMR and receives desatinib with good tolerance.

TKI resistance is defined based on the European LeukemiaNet (ELN) recommendations [3]. Resistance is divided into primary and secondary categories. Primary resistance is characterized by any of the following: no complete hematological response or Philadelphia-positive (Ph+)

*Address for correspondence: Katarzyna Martyna Pawelec, Department of Pediatric Hematology and Oncology and Clinical Transplantology, Warsaw Medical University, Warszawa, Poland, e-mail: katpawelec@poczta.onet.pl

Received: 25.04.2023 Accepted: 18.05.2023 Early publication date: 06.08.2023

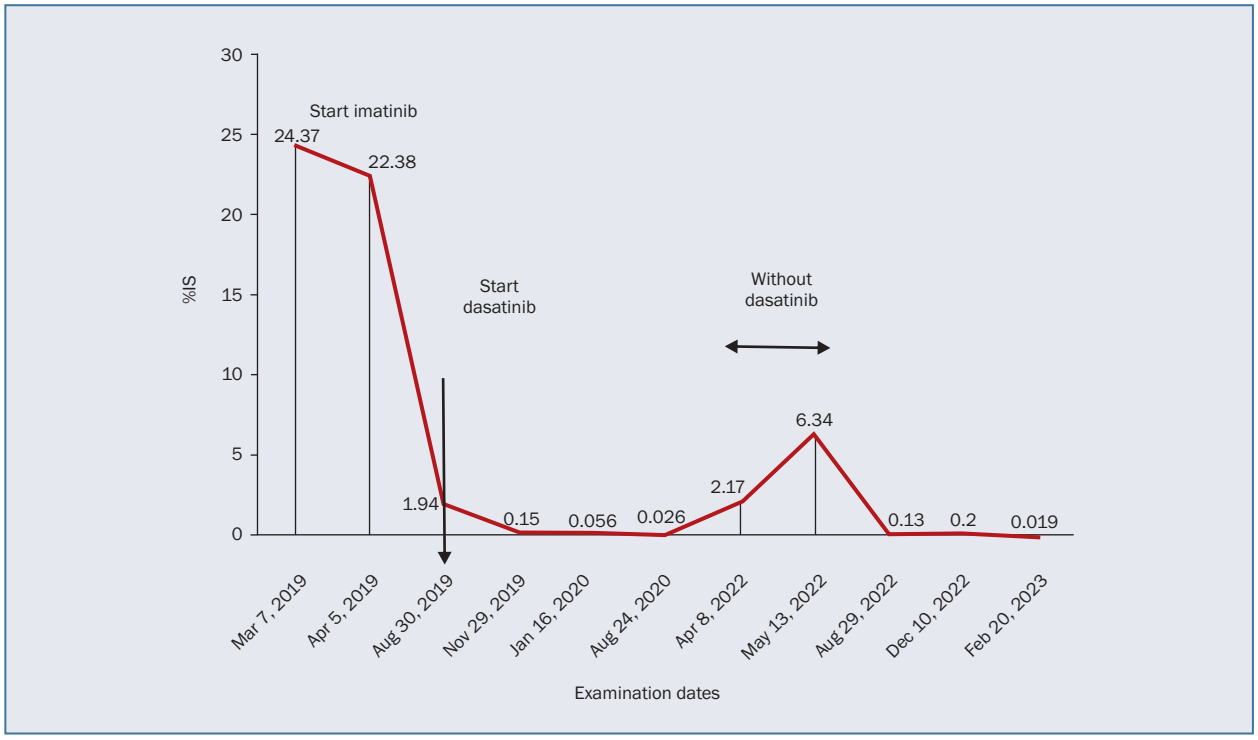

Figure 1. Monitoring BCR-ABL1 real-time quantitative polymerase chain reaction in blood during tyrosine kinase inhibitor therapy; IS — International Scale

>95% by three months, *BCR-ABL1* >10%, or Ph+ >35% by six months, or *BCR-ABL1* >1%, Ph + ≥1% or complete cytogenetic response by 18 months [10]. Secondary resistance is defined by the loss of a previously documented hematological, cytogenetic or molecular response [1–5]. TKI resistance has been reported in 25–30% of patients initially treated with imatinib [5, 6]. Most mutations in the KD, including p.G250E, p.Y253H and or p.E255K/V, can lead to the development of resistance to TKI therapy. The most common mutation in CML patients is T315I (15%), followed by phosphate-binding loop mutations E255K (11%), G250E (10%), and Y253H (10%) [9]. Thus, the detection of mutations can aid with the optimal selection of TKI and influence the prognosis of patients with CML, who can be switched to different TKIs based on the detected mutation [1, 7, 8].

In accordance with these recommendations, we performed a test for mutations in our patient. Thanks to the detected mutation with the assessment of sensitivity to TKI, we used desatinib in our patient with a good effect. However, in the case of a loss of a previously achieved response, the question should be asked: is the patient actually taking the medicine?

Authors' contributions

All authors have made a substantial, direct and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare no conflict of interest.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Hijiya N, Suttorp M. How I treat chronic myeloid leukemia in children and adolescents. Blood. 2019; 133(22): 2374–2384, doi: 10.1182/blood.2018882233, indexed in Pubmed: 30917954.
2. Lewandowski K, Lewandowski J. Chronic myeloid leukemia: where do we stand, where can we go? Acta Haematol Pol. 2022; 53(3): 153–165, doi: 10.5603/ahp.a2022.0012.
3. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34(4): 966–984, doi: 10.1038/s41375-020-0776-2.
4. Shima H, Shimada H. Recent progress in the management of pediatric chronic myeloid leukemia. Int J Hematol. 2023; 117(2): 182–187, doi: 10.1007/s12185-022-03526-2, indexed in Pubmed: 36574169.

5. Liu J, Yang H, Xu X, et al. Mutations in the BCR-ABL1 kinase domain in patients with chronic myeloid leukaemia treated with TKIs or at diagnosis. Oncol Lett. 2020; 20(2): 1071–1076, doi: 10.3892/ol.2020.11650, indexed in Pubmed: 32724345.
6. Lee H, Basso IN, Kim DD. Target spectrum of the BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia. Int J Hematol. 2021; 113(5): 632–641, doi: 10.1007/s12185-021-03126-6, indexed in Pubmed: 33772728.
7. Carofiglio F, Lopalco A, Lopedota A, et al. Bcr-Abl tyrosine kinase inhibitors in the treatment of pediatric CML. Int J Mol Sci. 2020; 21(12), doi: 10.3390/ijms21124469, indexed in Pubmed: 32586039.
8. Hamdan L, Hussein F, Akel S. Assessment of two main therapeutic regimens of chronic lymphocytic leukemia in a major referral center in Syria. Acta Haematol Pol. 2022; 53(4): 277–284, doi: 10.5603/ahp.a2022.0036.
9. Kim H, Kim S, Kim HJ, et al. Comparison of frequency and sensitivity of BCR-ABL1 kinase domain mutations in Asian and white patients with imatinib-resistant chronic-phase chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2018; 18(10): e391–e399, doi: 10.1016/j.clml.2018.06.031, indexed in Pubmed: 30082224.