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Case report

Chronic-phase chronic myeloid leukemia: Not always a reassuring diagnosis

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ABSTRACT

Primary resistance to tyrosine-kinase inhibitors (TKIs) is quite uncommon in chronic-phase Chronic Myeloid Leukemia (CML) and related to still poorly understood mechanisms, as ABL mutations are rarely detected in primary resistant patients. We report the challenging case of a CML patient who was resistant to multiple TKIs because of different emerging ABL mutations and became pregnant while on Nilotinib therapy despite repeated and clear discouragement to conceive. She decided to continue with her pregnancy, showing an admirable and incredible perseverance in the pursuit of her personal aims.

1. Case report

Imatinib has radically changed prognosis in chronic-phase Chronic Myeloid Leukemia (CML), with 90% overall survival rate at 8 yrs, and 40–70% of patients achieving a stable MMR [1]. Even better results have been reported in terms of cytogenetic and molecular responses and the rate of progression to accelerated/blast phase using second-generation tyrosine-kinase inhibitors (TKI) first-line [2,3]. Physicians are no longer familiar with resistant chronic-phase CML and are particularly frustrated when facing primary resistance to TKIs, as it is quite uncommon and related to still poorly understood mechanisms. Point mutations within the BCR-ABL kinase domain account for 50–60% of cases of secondary resistance to Imatinib and to a lesser extent to secondary resistance to second-generation TKIs [4]. However, ABL mutations are less frequently detected in primary resistant patients and mutational analysis is not required by European LeukemiaNet (ELN) Recommendations at diagnosis [5]. We report a CML patient who showed resistance to multiple TKIs because of different emerging ABL mutations, but who showed an admirable and incredible perseverance in the pursuit of her personal aims.

Our patient (a 24-year-old woman) arrived in Italy from Eastern Europe in March 2013 as an illegal immigrant. Three months later she was admitted to our hospital. Her blood counts were as follows: leukocytes 410.7 $\times 10^9$/L, platelets 391 $\times 10^9$/L, Hb 11 g/dl, with immature myeloid cells at differential count. Splenomegaly was palpable 4 cm below costal margin. Cytogenetic analysis on the bone marrow aspirate revealed t(9;22)(q34;q11) in 20/20 metaphases without additional abnormalities, and a BCR-ABL rearrangement (e14a2) was detected by qualitative RT-PCR. Chronic-phase CML was diagnosed as low risk according to Sokal score. Two leukapheresis procedures were performed and cytarabine (800 mg for two doses) was administered. Twenty days after admission Imatinib therapy was started at the dose of 400 mg OD. At this time the blood counts were: leukocytes 37.4 $\times 10^9$/L, platelets 551 $\times 10^9$/L and Hb 12 g/dl. An ABL mutational analysis was performed, although it was not required according to ELN Recommendations in chronic phase at diagnosis, and an F317L mutation was detected by Sanger sequencing. This mutation is resistant to dasatinib and sensitive to Imatinib albeit with higher IC50 than wild type ABL. Accordingly, the Imatinib dose was increased to 400 mg BID, but two months later hematologic response was still inadequate. Considering the low age and the poor response we applied for Nilotinb availability to treat our patient, although she was living in Italy without regular assistance from the National Health System. Nilotinib therapy was authorized by local Regulatory Agency and was started in September 2013 at the dose of 400 mg BID. A complete hematologic response was achieved, but after three months of therapy the BCR-ABL transcript level was still high (BCR-ABL/ABL 23% IS) without any cytogenetic response. The mutational analysis was repeated and two further mutations (F359V, E255V) both resistant to Nilotinib were discovered. A switch to Ponatinib therapy was planned (according to an individual use program) but at the end of January 2014 the patient communicated to be pregnant, despite repeated and clear

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discouragement to conceive. Nilotinib was immediately discontinued (6 weeks gestation) and elective abortion was suggested, because of risk of fetal abnormalities and refractory disease requiring treatment. The patient initially agreed; however, just prior to undergo the procedure she decided to continue with her pregnancy, due to her own religious beliefs and desire of motherhood. In the meanwhile, the WBC had increased to 101×10^9/L. Two leukapheresis procedures were performed resulting in a decrease in the WBC to 40×10^9/L. A spontaneous and unexpected lowering of leukocyte count was observed that allowed the patient to remain without treatment until May 2014. Then, IFN treatment was refused by our patient and Hydroxyurea therapy was started to control the disease (22 weeks gestation). A follow-up with ultrasound scan during the course of the pregnancy was unremarkable. Pregnancy was uneventful and at 36 weeks gestation a healthy male infant was born after induction of delivery (weight: 2.4 Kg). The infant was well and no developmental abnormalities were detected. Lactation was inhibited and Ponatinib was started (45 mg OD). At this time, cytogenetic analysis showed 8/8 Ph-positive metaphases; BCR-ABL transcript level was 63% IS and a double BCR-ABL rearrangement was detected by FISH analysis. Sanger sequencing showed F317L and F359V mutations. The patient is still on Ponatinib at the dose of 15 mg OD due to recurrent grade III cytopenia and the transcript level was 4.28% IS at the last check-up. The patient has two younger sisters (17-year old twins) and one brother who are not allowed to move to Italy and could therefore not be tested for the HLA compatibility. A full-matched HLA identical unrelated donor has been identified, but the patient decided to postpone the allogeneic transplant as she is not able to manage the predictable issues related to the procedure in the absence of an adequate familial support.

In this case we had to face two serious concurrent problems: refractory CML and conception under second-line TKI. Primary resistance to TKIs entails a very dismal prognosis. In our case ABL mutations selected in sequence by the TKI in use were apparently responsible for resistance to multiple TKI, but in addition genetic instability typical of a more advanced phase might be hypothesized in a patient who had most likely ignored her disease for months. Ponatinib has been proven to be effective in heavily pretreated CML patients independent of the presence of ABL mutations [6]. However, genetic instability makes a long lasting response quite unlikely. Allogeneic stem cell transplantation seems to be the only meaningful option in this case, but we do not know if our patient will ever undergo the procedure. Whereas some reassuring data exists on unplanned conception under Imatinib treatment [7,8], very little information is available about the safety of conception under Nilotinib [9,10], and female patients in reproductive age are strongly advised to use effective methods of contraception while receiving TKIs. Fortunately, the child is healthy and developing normally. In our case the management of the pregnancy posed challenges to both the patient and the physicians, as our patient became pregnant on Nilotinib while strictly requiring treatment to control her disease. Moreover, it required delicate attention to important ethical and psychosocial issues, including as well as cultural sensibilities. So far, the patient has been confident in the good outcome of the whole clinical course, often reassuring her increasingly worried physicians with a smile and pictures of her son. This case reminds us that (i) CML is still a life-threatening disease and we should not to lower our guard, despite excellent results in the majority of patients and multiple TKIs available; (ii) patients' personal social contexts and wishes have to be respected, even if they contrast with rational adherence to the treatment guidelines; and (iii) a patient's perseverance and optimism are invaluable in the fight against leukemia.

Conflict of interest

CE and SZ declare no conflict of interest. EMO: speaker bureaus of Novartis, Brystol-Myers Squibb, ARIAD Pharmaceuticals.

Authors' contributions

E.M.O. and C.E. were responsible for the clinical management of the patient, acquisition of data, drafting the manuscript. S.Z. was responsible for Sanger sequencing. All authors read and approved the final manuscript.

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