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Case Report
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Blast Crisis of CML After TKI Discontinuation in a Patient With Previous Stable Deep Molecular Response: Is It Safe to Stop?

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During the last decade many studies have addressed the issue of stopping TKI treatment in patients with stable deep molecular Response (MR4 or MR4.5).[1,2] In these studies, treatment discontinuation proved a safe option, since new major molecular response is achieved in all cases with TKI rechallenge. Treatment-free remission (TFR) is an arising option in standard care, due to issues regarding the patient, that is, side effects or quality of life, and becomes a possibility outside clinical trials,[3] especially when reinitiation of the treatment seems to guaranty a new molecular cure. Despite the cumulating data, safety of this choice remains an issue for physicians. We report here a case of lymphoid blast crisis originating from a nilotinib resistant clone 6 months after reinitiation of the drug for molecular relapse post a TFR period, outside the context of a clinical trial. This is to our knowledge the second patient who experiences a blast crisis in this context.[4]

Our patient is a 69-year-old female who was diagnosed with CML in 2005 in first chronic phase, with a low sokal score and imatinib treatment was started in standard dose. At 3 months she achieved a molecular response (MR) of 2.1% (IS was not available at the time), at 6 months her MR was 0.44%, with complete cytogenetic response and MMR was reached in 18 months, optimal response according to the 2006 ELN guidelines. Arthritis and anemia attributed to imatinib were easily managed with proper treatment but 2 episodes of pericarditis led to the change of treatment to second-generation TKI (600 mg of nilotinib daily) in 2011. Twelve months later the patient achieved deep molecular response (MR4–MR4.5) stable for 3 years. During the treatment with nilotinib the patient presented with atrial fibrillation, diagnosed after a transient ischemic attack, and a new episode of pericarditis. At that point, discontinuation of the drug was discussed. In 2015, 9 years after diagnosis and whilst 2 years on MR4 and the last year in MR4.5, nilotinib was stopped. The patient was regularly monitored and she remained in DMR until 18 months off treatment, when for the first time, MR4 was lost (MR: 0.02% IS). A subsequent sample in 2 months revealed a loss of MMR (MR: 12% IS). Nilotinib was restarted and MR4 was soon achieved. However, 6 months later, the patient presented with anemia and thrombocytopenia. Diagnostic reevaluation with a bone marrow aspiration showed infiltration with 90% of lymphoid blasts. A clonal evolution with deletion of the short arm of chromosome 3 [46, XX, del(3)(p21;p23), der(9)t(9;22)(q34;q11)t(9;22)(p12;q11),der(22)t(9;22)(q34;q11)t(9;22)(p12;q11)[22]] was found in cytogenetic analysis. Mutational analysis with Sanger Sequencing revealed a nilotinib resistant mutation (c.757T>C, Y253H), which was not present at the time of molecular relapse. Due to high comorbidity Index she received low toxicity chemotherapy (high dose dexamethasone and vincristine) and ponatinib. She is currently, 3 months after the treatment, in DMR.

Several trials have tested the safety of discontinuation of treatment with TKI's when patients remain for years in a DMR, making the option of TFR feasible for patients in standard practice.[1,2,5,6] In the current recommendations for nilotinib discontinuation, MR4.5 lasting for at least 1 year is required and our patient, who stopped the treatment because of side effects, fulfilled at the time these criteria. Recent recommendations have been published on how to monitor these patients.[3] Frequent monitoring is required during the first year when most (95%) of the molecular relapses have been observed. Early relapses are characterized by an exponential increase in BCR-ABL1, rising by 0.5 to 1 log per month. Thereafter less frequent assessments can be made and 3-monthly tests suffice.[7] Our patient experienced a molecular relapse 18 months after the cessation of the treatment

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under a regular monitoring. The threshold of molecular relapse in which retreatment is required has been proven to be loss of MMR in recent trials.[4] Our patient was retested early upon reappearance of molecular burden and once MMR loss was confirmed, she reinitiated treatment with TKI. New molecular responses are achieved on rechallenge with TKI. Our patient achieved an early MR4, but soon presented with a blast crisis. Only one such case has been reported to our knowledge, when CML progressed to a lymphoid blast phase characterized by cytogenetic clonal evolution after imatinib resumption in a patient from the A-STIM study.[4] In the last case blast crisis was documented also after the achievement of MMR and "sudden blast crisis" was postulated. Our second reported patient indicates that maybe this is not the case. Blast phase was initiated from a nilotinib resistant clone. Since TKIs cannot eradicate CML from leukemic stem cells,[8] currently there can be no cure of the disease outside the context of allo-HCT.TKI treatment leads to the selection of different leukemic clones than the first originating the disease and persisting leukemic clones continue to exist in a milieu of immunosuppression and in some cases drive the relapse.[9] Reinitiation on the same TKIs has always been successful. To our knowledge only one case has been reported with a mutation resistant to the TKI, in a patient enrolled in the first line nilotinib discontinuation trial, ENESTfreedom,[5] when MMR loss was accompanied by the detection of a nilotinib-resistant F359V BCR-ABL1 kinase domain mutation. In our case mutational analysis with Sanger Sequencing did not detect the Y253H mutation at the time of relapse supporting the hypothesis that it developed later under nilotinib selection. This raises the question of the choice of TKI after the molecular relapse: until recently the same TKI is recommended, however the appearance of a nilo-resistant clone is bringing in light the option of sequential treatment. In conclusion, we report the first blast crisis with a nilotinib resistant clone, after a regain of MMR in the setting of nilotinib discontinuation outside a clinical trial. More data from real-world practice in discontinuation of TKIs can give clinicians a better aspect of safety of this tactic.

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