A Treatment-free Interval Allowed by Ponatinib as Fourth-line Therapy

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Abstract. Background: The third-generation tyrosine kinase inhibitor ponatinib has demonstrated high clinical efficacy in the setting of patients with resistant chronic phase chronic myeloid leukemia (CML), also inducing deep molecular responses. However, ponatinib-related cardiovascular toxicities make management challenging, especially of those patients with CML with previous cardiovascular comorbidities. Case Report: We report on the efficacy of ponatinib treatment used as fourth-line therapy in a 55-year-old woman affected by significant comorbidities (mainly cardiovascular) present before the diagnosis of CML. Ponatinib therapy induced a rapid and excellent clinical response, with the achievement of a durable deep molecular response that allowed us to propose a strategy of treatment discontinuation in order to reduce drug-related toxicities. Conclusion: A strategy of a treatment-free interval might represent a useful clinical tool in those patients with CML who achieve a durable deep molecular response but are also affected by significant comorbidities in order to minimize the risk of ponatinib-related toxicities.

The prognosis of chronic myeloid leukemia (CML) has been radically changed by the introduction of therapy with tyrosine kinase inhibitors (TKIs), which have led to unprecedented rates of complete haematological and cytogenetic responses, as well as sustained reductions in breakpoint cluster region-Abelson (BCR-ABL1) transcript levels (1). TKI therapy has shown so effective that the treatment goal for many patients is no longer the simple molecular remission with a three-logarithmic reduction but a deep molecular remission (DMR), which can be so profound that treatment can be discontinued. Therefore, the achievement of these impressive clinical results has led to the prospect of ‘treatment-free remission’ (TFR), i.e. the possible discontinuation of treatment, as a new clinical endpoint in CML management and therapy (2). In fact, evidence has shown that most patients who have achieved a stable DMR can safely discontinue TKI treatment (3-5). Unfortunately, not all patients with CML treated with TKIs achieve an optimal response according to the European LeukemiaNet recommendations and a proportion of them have to change TKI therapy for this reason or due to intolerance to treatment (6, 7). In the latter CML scenario, both second- and third-generation TKIs have demonstrated high efficacy, including the achievement of a DMR.

The third-generation TKI ponatinib has become a valid treatment option in the setting of patients with CML resistant or intolerant to previous therapies, having also shown activity against the BCR–ABL1 T315I mutation (8) and being suggested in the pursuit of new therapeutic strategies aiming for TKI discontinuation (9).

Herein we report on the efficacy of ponatinib treatment used as fourth-line therapy in both inducing a durable DMR and a feasible treatment discontinuation interval. This treatment-free interval (TFI) allowed us to reduce ponatinib-related toxicities in a patient with previously resistant chronic-phase CML (CP-CML) affected by different and severe comorbidities before her diagnosis.

The patient provided written informed consent allowing us to anonymously report her clinical case.
Case Report

A 55-year-old woman was admitted to our Hospital in October 2011 because of leukocytosis and thrombocytosis. Physical examination did not show hepato-splenomegaly nor lymph node enlargement. Blood tests revealed a white blood cell count 17.04×10⁹/l, a platelet cell count of 1.848×10¹²/l, a haemoglobin concentration of 11.8 g/dl and altered lactic dehydrogenase level (765 U/I). The differential white blood cell count showed the presence of immature myeloid circulating cells (metamyelocytes, myelocytes, and promyelocytes) in the absence of blasts. Conventional cytogenetic analysis detected the presence of the Philadelphia-positive chromosome in 40% of the examined metaphases, with no additional abnormalities. The patient was then diagnosed as having CP-CML, with an e13a2 BCR–ABL1 transcript. The BCR-ABL1/ABL ratio was 133.58% according to the international standardized scale (IS) (10).

Calculated parameters of CML risk at diagnosis (6) were: high Sokal risk, high EURO score and low scores for both European Treatment and Outcome Study and Long-Term Survival. The following comorbidities were present before the diagnosis of CP-CML: cardiovascular diseases (hypertension, atherosclerosis of the superaortic trunk), dyslipidaemia and non-insulin-dependent diabetes mellitus.

After informed consent and a preliminary cytoreduction with hydroxyurea, the patient was started on conventional imatinib therapy and soon achieved a complete haematological response, a complete cytogenetic response (CCyR) and a major molecular response (MMR or MR3) after 3 months of treatment. However, while on imatinib-therapy, the patient developed drug-induced intolerance (diffuse and persistent chronic muscle cramps, of grade I-II) and imatinib therapy was stopped. Dasatinib treatment (100 mg daily) was then administered as second-line therapy. Within 6 months, the patient achieved a DMR and maintained an optimal response (either MR4 or MR4.5) until September 2016 when, after more than 4 years on dasatinib therapy, she lost both DMR and MMR (BCR–ABL1 IS 2.5%). Sequencing of the BCR–ABL1 tyrosine kinase domain, after cloning of the polymerase chain reaction amplification product, isolated the E450G mutation in 10% of the clones. Cytogenetic analysis still revealed a CCyR, nevertheless a donor search for a bone marrow transplant was activated. During the course of these lines of TKI therapy, the patient was monitored for her pre-existing comorbidities.

In October 2016, the patient was started on bosutinib (500 mg daily) as third-line therapy. Unfortunately, 1 month later, due to bosutinib-related intolerance (abdominal pain and diarrhea, both grade II), fourth-line therapy with 45 mg ponatinib daily was commenced. During ponatinib treatment, the patient achieved a rapid and excellent molecular response, obtaining MR4 after 1 month and MR4.5 thereafter. As a consequence, the ponatinib dose was lowered to 15 mg daily and treatment was maintained for 26 months. At that time, because of both sustained MR4.5 and the presence of the comorbidities, and after discussing issues on discontinuing treatment with the patient, ponatinib therapy was stopped. The patient enjoyed a TFI in DMR (either MR4 or MR4.5) for 12 months. In February 2020 a reduced molecular response was detected (MR3) and 1 month later, DMR was lost (BCR–ABL1 IS 0.1%). Therefore, ponatinib treatment was resumed and MR4.5 was achieved again within 3 months of therapy. The patient currently remains in DMR, under strict molecular monitoring and on therapy with a low ponatinib dose. A multidisciplinary approach is ongoing for the other diseases with no worsening of cardiovascular diseases.

Discussion

We describe the case of a female patient with CML who enjoyed a TFI from ponatinib therapy for 12 months. Her fourth-line TKI therapy was stopped after the achievement of a sustained DMR mainly because of the pre-comorbidities existing before the diagnosis of CML. In fact, although this patient did not adequately meet current CML requirements for TKI discontinuation (2-6, 11) there was a strong clinical need in reducing ponatinib-related toxicities, mainly because of the pre-existing cardiovascular diseases. As is evident, nilotinib treatment did not represent a useful therapeutic option in this clinical context.

In this scenario some biological factors may have played a role in allowing a TFI from TKI therapy. Firstly, the patient never lost the complete haematological response, or CCyR, nor CP-CML. Moreover, she had achieved an optimal response to frontline TKI therapy, although becoming intolerant to imatinib thereafter. Secondly, she showed a secondary type of CML resistance (acquired with dasatinib therapy) with the emergence of the E450G mutation in the BCR–ABL1 kinase domain (12). This mutation is located in the C-terminal of BCR–ABL1 and outside of both the phosphate-loop and activation-loop, and seems to be less frequent in patients with CML receiving TKIs (13) and having a minor proliferative activity. Thirdly, ponatinib treatment, which has been reported to induce both CCyR and molecular responses in patients with resistant CML or who are intolerant to previous therapies (8, 9), demonstrated an excellent clinical efficacy in eliminating the mutation and again achieving a DMR.

TFR has emerged as a therapeutic goal in therapy of CML (2-6,11, 14, 15), however, whether the opportunity for TKI discontinuation might be extended to other settings of CML is currently undefined. Sometimes TKI therapy must be discontinued to reduce or resolve adverse events (7), and the presence of toxicities has been described among the reasons...
for stopping TKI therapy in real-life management of CML (16). The toxicity of some TKIs, particularly ponatinib, is not negligible, especially in patients with previous cardiovascular disease. It is likely that continuous therapy over many years may induce significant damage of the cardiovascular system. With this view, some therapeutic strategies evaluating ponatinib dose reduction after achieving a molecular response are currently under investigation (17).

The favourable evolution of our clinical case might lead to the exploration of a new therapeutic strategy for which, once a DMR has been obtained, ponatinib therapy might be discontinued and then resumed after losing MMR. This ‘stop and go’ strategy could contribute in reducing the severity of side-effects of the drug, especially in patients at high risk of vascular complications. In conclusion, similarly to TFR, TFI side-effects of the drug, especially in patients at high risk of cardiovascular complications. In conclusion, similarly to TFR, TFI might be considered as a useful clinical tool in those patients with CML who achieve durable DMR but are affected by significant comorbidities (mainly cardiovascular) in order to reduce or prevent TKI-related toxicities in the long term.

Conflicts of Interest

These Authors declare the following conflict of interest: FS, honoraria by Bristol-Myers-Squibb, Incyte, Novartis, Pfizer; FDR, honoraria by Amgen, Bristol-Myers-Squibb, Celgene, Incyte, Novartis, Pfizer. All other Authors report no conflicts of interest regarding the article. The Authors alone are responsible for the content and writing of the article.

Authors’ Contributions

AB, UM, CB, CC and FS contributed substantially to draft writing, SS performed laboratory tests, and FDR and FS contributed significantly to reviewing. All Authors have seen and approved the final version of the article.

References


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