HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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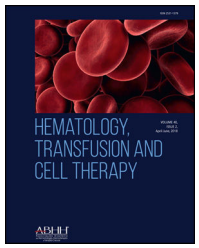

Case Report

Experience using Imatinib and then Nilotinib, as second line, in patient with chronic myeloid leukemia and previous bariatric surgery. A case report

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ARTICLE INFO

Article history:
Received 1 July 2019
Accepted 23 September 2019
Available online 14 November 2019

Chronic myeloid leukemia (CML) has become a model of success in the history of hematology. That is due to the possibility of discovering and monitoring the molecular basis of the disease and blocking it by employing tyrosine kinase inhibitors (TKIs).[1] In the beginning of the XXI century, chemotherapy and the recombinant interferon-alpha were overcome by the efficiency of the TKIs in chronic-phase (CP) CML patients. Approximately 80% of the patients presenting CP-CML treated with imatinib achieved complete cytogenetic remission (CCR). Moreover, these patients also present extraordinary long survival rates. Firstly, imatinib demonstrated that a fatal cancer could become a chronic comorbidity. Soon after the first generation of TKIs, owing to the development of imatinib-resistance, other TKIs were developed, such as: dasatinib, nilotinib, bosutinib and ponatinib.

The TKI era has modified the CML treatment and its outcomes consensus was reached regarding rational goals to define optimal response, based on time to CCR and molecular response (MR).[2] Thus, it was possible to adopt intervention patterns for patients who failed to respond adequately to regular treatment.[3]

Currently, optimal response is considered when patients achieve major molecular response (MMR), BCR-ABL1 $\leq$ 0.1% on the International Scale (IS) within 12 months of the TKI treatment.[2,3] Molecular response levels have been related to the best control of the disease and long survival. Nilotinib has displayed better efficacy than imatinib in achieving MMR within two years.[4] Deep molecular response (DMR), defined as a 4.5 log reduction (IS), has been the real target response in order to promote the discontinuation of the TKI.[5] Several

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https://doi.org/10.1016/j.htct.2019.09.003

studies have shown that it is feasible to discontinue treatment after at least two years of DMR. On the other hand, it is important to know that treatment-free remission ranges from 48 to 67%.[5]

In Brazil, imatinib is the TKI generally used in the first-line treatment for patients with CP-CML. Although the importance of imatinib has been recognized, 20–30% of the patients discontinue treatment because of imatinib-related unsatisfactory response, resistance or toxicity.[6] Nilotinib has shown significant improvements (45% achieved CCR) for patients who are resistant or intolerant to imatinib.[7] Instead of evaluating solely the imatinib treatment efficacy, another aspect of patient monitoring comprises the imatinib-related adverse events (IRAEs). Today, due to the long-lasting character of treatments, not only adverse events grade III–IV have been the reason to switch to other TKIs, but also mild and moderate adverse events that are linked with the quality of life.[9] The IRAEs from imatinib are frequent[1] and more predominant, compared to nilotinib.[9] It has been reported that it is possible to reduce or resolve the IRAEs after three months of shifting to nilotinib.[10] Thus, it is important that Brazilian patients be closely monitored, with analysis of the quality of life, adherence and their relation to IRAEs. Consequently, for patients treated with imatinib, switching to nilotinib has been indicated, due to the resistance to imatinib, failed optimal response and intolerance.

Our purpose, therefore, is to describe the importance of switching the treatment, in an unknown scenario of previous bariatric surgery, to the optimal response by imatinib, however with poor quality of life due to chronic IRAEs.

In September 2014, a 67-year-old female patient presented with leukocytosis in a routine blood count of leukocytes at 15.9×10^9/L, with neutrophilic predominance and 570,000 platelets/mm^3. She was asymptomatic and no splenomegaly was palpable. Cytogenetic analysis showed 46, XX, t(9;22) (q34.1;q11,2) [16]/46, XX[4]. The patient was diagnosed with PC-CML, classified as intermediate risk by the Sokal index. The patient's medical history included Roux-en-Y laparoscopic gastric bypass for weight loss in 2002, arterial hypertension and hypothyroidism.

The Conventional dose of imatinib of 400 mg/day was initiated in December 2014. After six months, the patient achieved CCR and BCR-ABL < 1% on the IS. In October 2015, the DMR was confirmed.

Despite good laboratorial response, she presented some clinical complaints. Her quality of life was harmed by considerable IRAEs: muscle cramps grade II, nausea grade II and pruritus grade I. Due to the DMR, her attending physician opted to maintain the imatinib treatment. However, in October 2016, blisters grade II appeared on both legs. Therefore, the doctor decided to switch to nilotinib as a second-line treatment.

In November 2016, nilotinib 400 mg twice/day was initiated, aspiring to reduce the IRAEs. All of the symptoms were resolved within six months, as she remained in DMR. Currently, her status remains asymptomatic and in DRM.

On that account, this case demonstrates that switching to nilotinib may fade chronic IRAEs, as well as conserving the DMR in a patient with bariatric surgery.

Discussion

This case presented adequate treatment adherence and optimal response, despite evidencing poor quality of life.

Although imatinib has shown to be safe and effective in the history of CML, chronic mild and moderate IRAEs are not rare.[8] In this case, her mild chronic IRAEs were frequent, since the IRIS trial revealed a high frequency of nausea, muscle cramps, and pruritus[1] (Table 1). Chronic mild and moderate IRAEs may negatively influence the quality of life and impact adherence to the imatinib therapy, which leads to less desirable outcomes.[11] Changing from imatinib to another tyrosine kinase inhibitor (TKI) may enhance tolerability and quality of life. The nilotinib treatment, compared to imatinib, exhibited less frequency of nausea, muscle cramps, vomiting and diarrhea.[9] In addition, the ENRICH study demonstrated that switching to nilotinib reduced 84.6%, and resolved 62.9%, of chronic IRAEs. Switching to nilotinib revealed to be acceptably safe and potent for molecular response[10] (Table 1).

Mild skin reactions are relatively frequent, ranging from 7% to 21% in patients treated with imatinib. Skin rashes are relatively common and may be resolved with oral steroids.[12] Cutaneous reactions to imatinib seem to be correlated with the dose.[12] The imatinib-related blister, a rare skin toxicity, is not well understood. However, the case of a female with a recurrent blister 1.5 years after initiating the imatinib therapy for a gastrointestinal stromal tumor (GIST) has been described. A laminin and collagen IV loss along the dermoepidermal junction was observed, suggesting that, in susceptible patients, imatinib diminishes the synthesis of laminin and collagen IV, resulting in a blister.[12] In our case, the blisters were resolved after switching to nilotinib.

This case study presented poor quality of life due to some IRAEs, while still displaying optimal response, but she did not qualify for the cessation of the TKI. Thus, switching to nilotinib was a reasonable option, in spite of the gastroplasty. There have been few studies regarding TKIs in patients with a history of bariatric surgery. Pavlowski et al. demonstrated in a case report that the imatinib concentration decreased 40–60% after sleeve gastrectomy. On the other hand, a patient remained in molecular response[13] in a similar scenario in which Yassin et al. described a female patient treated with dasatinib who lost hematological response after a sleeve gastrectomy, with negative mutation analysis. After switching the treatment to imatinib, she achieved an adequate response. In another case, a male was diagnosed with CML two years after undergoing a sleeve gastrectomy. The treatment started with nilotinib 300 mg q12 h, but the patient did not achieve a cytogenetic and molecular response, presenting a negative mutation test. After switching the treatment to imatinib, he achieved a molecular response.[14] Liu and Artz observed the reduction of imatinib levels from 956 to 156 ng/mL after a Roux-en-Y gastric bypass in a study subject. This patient did not achieve a DMR by employing imatinib. Nilotinib was described as the second-line treatment, but no outcome from that treatment has been described.[15] Even though these cases are anecdotal, evidencing failure in the second-generation TKIs, our case report expressed the successful choice of nilotinib treatment,

Table 1 – Imatinib-related adverse events (IRAEs) presented in this case: incidence, rate of resolution after switching to nilotinib.

IRAE	IRIS trial[1] IRAE all grade $n = 551$	ENRICH study[10] Resolved IRAE After 3 months of switching to nilotinib n (%)	Case report Status of IRAE after switching to nilotininb
Muscle cramps	38.3%	9 (100%)	Resolved
Nausea	43.7%	15 (93.7%)	Resolved
Pruritus	3.1%	2 (66.6%)	Resolved

applying a 400 mg q12 h posology after the DMR, achieved by imatinib.

Therefore, this case report presents common IRAEs, which determined a poor quality of life, in contrast with no loss of adherence regarding the DMR (Table 1). This case deserves to be registered in order to emphasize that a patient was successfully treated with nilotinib 400 mg q12 h, even while presenting a Roux-en-Y gastric bypass. Such treatment strategy presented maintenance of the DMR and resolution of IRAEs, including the gastrointestinal adverse events, even when administering the nilotinib posology twice a day.

Conflicts of interest

The authors declare no conflicts of interest.

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