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Letter to the Editor

The spectrum of musculoskeletal symptoms in patients with chronic myeloid leukemia after stopping tyrosine kinase inhibitors

1. Introduction

Chronic myeloid leukemia (CML) accounts for 10–15% of new leukemia cases and has an incidence of 1–2 cases per 100,000 adults [1]. The hallmark of the disease is the presence of a reciprocal translocation between chromosome 9 and 22, t(9;22)(q34;q11), also known as the Philadelphia chromosome [2]. This gives rise to the *BCR-ABL1* fusion gene which produces a BCR-ABL1 fusion protein with constitutive tyrosine kinase activity, resulting in uncontrolled expansion of myeloid elements [2]. Left untreated, CML inexorably progresses from a chronic phase to the more aggressive accelerated and terminal blast phases [2].

With the advent of BCR-ABL tyrosine kinase inhibitors (TKIs), long term survival of chronic phase patients is more than 80% and approximates that of age matched controls [3]. Due to the high cost of TKIs [4] and diminished quality of life in a significant subset of patients on chronic treatment [5], discontinuing therapy is appealing [6–10]. Results reported from the STIM [11] and TWISTER [12] prospective trials show that 41–47% of patients who had undetectable BCR-ABL transcript levels for at least 24 months may remain in persistent major molecular response (MMR) after cessation of imatinib. Molecular relapse occurs mainly in the first 6 months after discontinuation, and TKI resumption is highly effective in restoring response [13]. Similar results were reported from the Euro-SKI study [14] and the French STOP 2G-TKI [15], assessing the cessation of imatinib, and nilotinib and dasatinib, respectively. Following the cessation of TKIs, reports of a so-called “TKI withdrawal syndrome” have been described, presenting as pains involving various joints [16,17]. We report on 9 pts with chronic phase CML, most of whom developed TKI withdrawal syndrome after cessation of TKI therapy.

2. Case presentations

We identified 9 patients seen at the KCI who discontinued TKI therapy. Of these 9 chronic phase CML patients with prolonged molecular remission (defined as undetectable polymerase chain reaction (PCR) for BCR/ABL, sensitivity 10^{-4}), five were being treated with imatinib, one with dasatinib, and one with nilotinib; one received nilotinib then dasatinib, and one was receiving dasatinib, following therapy with imatinib and nilotinib. Five patients were experiencing significant side effects from their TKI treatment, three requested discontinuation and the ninth was planning for pregnancy. Five patients were male, eight were Caucasian and one was Black. The median age at diagnosis of CML was 48 years (range: 26–55 years). The median duration of TKI therapy before discontinuation was 10 years (range: 2–13.5). All but one patient had undetectable transcripts for 2 years or more.

Seven of nine patients developed musculoskeletal complaints with arthralgias and joint stiffness after cessation of TKIs. The pattern and location of involved joints was variable and most patients reported symptoms in multiple areas simultaneously. The joints were usually not swollen, erythematous or tender to palpation on examination. Three patients had osteoarthritic pain of the lumbosacral spine prior to cessation of TKIs; however, none of these patients had exacerbation in these joints after cessation of TKIs. Arthralgia was Grade 1 in three patients, and Grade 2 and 3 in one and three patients, respectively, based on the Common Terminology Criteria for Adverse Events scale (version 4.0). Interestingly, many patients did not mention these complaints except after specific questioning, including one who had visited an emergency room because of this discomfort and another who scheduled a consultation with a rheumatologist. The median duration from TKI cessation to the occurrence of symptoms was 1.5 months (range: < 1–6 months). Three of the seven patients who developed arthralgias underwent rheumatological work up that included imaging as well as laboratory tests (including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, cyclic citrullinated protein, antinuclear antibody (ANA), and complement); however, those tests were nonrevealing.

All symptomatic patients initially self-medicated with nonsteroidal anti-inflammatory drugs (NSAIDs) prior to seeking medical care regarding their arthralgias. Five of the nine patients experienced molecular relapse of CML. Of those, two had arthralgias that improved with resumption of TKIs; another patient remained asymptomatic. The fourth patient developed significant arthralgias approximately one month after cessation of nilotinib. She responded minimally to NSAIDs and required several short courses of corticosteroids for relief. She was started on imatinib upon relapse but continued to have significant arthralgias for about 4–5 months which have finally begun to resolve. Lastly, one patient has required continuous therapy with corticosteroids to ameliorate his peri-articular and musculoskeletal symptoms. His symptoms did not improve after resuming TKI therapy with low dose imatinib and subsequently 20 mg of dasatinib, both started while he was still in molecular remission, and there was also no benefit from trials of hydroxychloroquine and tofacitinib, a JAK2 inhibitor. He then experienced a late molecular relapse of his CML ~ 18 months after discontinuation. Because of problems with pleural effusion, higher doses of dasatinib could not be tried and he is currently receiving bosutinib, 400 mg daily. He regained remission, but after 4 months of therapy, his symptoms persist, and he continues to require a small dose of 5 mg prednisone daily.

Four of the nine patients who stopped TKI therapy remain in molecular remission. Of those, one continues to be symptom-free, and two had spontaneous resolution of their MSK symptoms within a few months. One had little benefit with corticosteroid therapy, and imatinib was resumed for the arthralgias. However, the subject discontinued treatment after a short course (16 days) due to side effects. She

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continues to experience mild symptoms.

3. Discussion

The use of TKIs in the treatment of chronic phase CML has fundamentally changed the prognosis of CML pts [3]. However, it is not without cost [4] or side effects [5]. In patients in whom TKIs were discontinued, a TKI withdrawal syndrome has been described, consisting of musculoskeletal pain involving various joints, but at times also presenting as muscle tenderness resembling polymyalgia rheumatica [16,17]. Rates of 20–30% have been reported [11,14,16,17], but the incidence of this syndrome might be underreported, owing to the retrospective allocation of such symptoms and the fact that the majority of presentations are low grade and therefore may not be collected by TKI cessation trials [18]. Similar to our observations, minor to no laboratory abnormalities were noted on previous reports of TKI withdrawal syndrome [16,17]. In Richter's report of fifteen Swedish patients participating in the EURO-SKI trial, two had minimally elevated CRP [16].

A longer duration of TKI treatment and a history of osteoarticular disease are potential predisposing factors [17], without a clear gender or age predominance. The cause of the TKI withdrawal syndrome remains unclear but might be related to re-expression of some of the other kinases which are suppressed by these pleiotropic TKIs. For example, c-Kit inhibition by TKIs reduces sensitivity to thermal pain, while c-Kit activation results in hypersensitivity to noxious heat, without altering sensitivity to innocuous mechanical stimuli [19]. Another possible mechanism relates to renewed activity of mast cells due to c-Kit reactivation with TKI cessation; this is consistent with the observation of improved asthma control in asthmatic patients with CML who were on TKIs [20]. Another possibility is a rebound phenomenon to the modulation of bone metabolism and electrolyte imbalances caused by imatinib [21].

No difference has been reported in the rate of molecular relapse within the first 6 months after cessation of therapy between patients who reported MSK symptoms and those who did not [16]. In previous publications, musculoskeletal symptoms resolved in 37% and 85% of patients after 3.5 weeks and 1–3 months, respectively, of resuming TKIs in those whose disease relapsed [16,17]. Of the five patients who experienced relapse in our cohort, four had reported MSK symptoms, while one was asymptomatic. The time from cessation of TKIs to relapse was 1, 3, 5, and 18 months in those who experienced symptoms, and 2 months in the one who was asymptomatic. The severity of symptoms falls into a spectrum. While the majority of patients will have mild to moderate arthralgias, we demonstrate three cases of grade 3 arthralgias, with persistent symptoms despite achieving remission of the CML.

It has been speculated that in some patients the continued control of CML after TKI cessation could be related to suppression of residual disease by the immune system. It is interesting to consider that in the patient with the very unusually late relapse, immunosuppression from chronic corticosteroids administered for prolonged withdrawal symptoms might have been permissive of the regrowth of the CML clone.

4. Conclusion

The etiology of the so-called TKI "withdrawal syndrome", which is loosely defined as musculoskeletal symptoms occurring after cessation of TKI therapy, remains unclear. The actual incidence of this syndrome has not been fully elucidated, and it seems to be underappreciated and perhaps under-reported by patients. Although most symptoms are relatively mild and self-limited, the possibility of developing a TKI "withdrawal syndrome" should be discussed with patients considering TKI discontinuation, particularly because these symptoms can be persistent in some individuals, even after restarting TKIs.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (1) (2018) 7–30.
[2] C.A. Schiffer, BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia, N. Engl. J. Med. 357 (3) (2007) 258–265.
[3] A. Hochhaus, et al., Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia, N. Engl. J. Med. 376 (10) (2017) 917–927.
[4] Experts in Chronic Myeloid, L, The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts, Blood 121 (22) (2013) 4439–4442.
[5] K.M. Phillips, et al., Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison, Support. Care Cancer 21 (4) (2013) 1097–1103.
[6] J. Aoki, et al., Sustained complete molecular response of chronic myeloid leukemia after discontinuation of second-generation tyrosine kinase inhibitors, Leuk. Lymphoma 53 (7) (2012) 1412–1414.
[7] J. Cortes, S. O'Brien, H. Kantarjian, Discontinuation of imatinib therapy after achieving a molecular response, Blood 104 (7) (2004) 2204–2205.
[8] J. Imagawa, et al., Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial, Lancet Haematol. 2 (12) (2015) e528–35.
[9] S. Mori, et al., Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study, Am. J. Hematol. 90 (10) (2015) 910–914.
[10] D.M. Ross, et al., Durable complete molecular remission of chronic myeloid leukemia following dasatinib cessation, despite adverse disease features, Haematologica 96 (11) (2011) 1720–1722.
[11] G. Etienne, et al., Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia, J. Clin. Oncol. 35 (3) (2017) 298–305.
[12] D.M. Ross, et al., Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study, Blood 122 (4) (2013) 515–522.
[13] S. Bhalla, D. Tremblay, J. Mascarenhas, Discontinuing tyrosine kinase inhibitor therapy in chronic myelogenous leukemia: current understanding and future directions, Clin. Lymphoma Myeloma Leuk. 16 (9) (2016) 488–494.
[14] F.-x. Mahon, et al., Cessation of tyrosine kinase inhibitors treatment in chronic myeloid leukemia patients with deep molecular response: results of the euro-ski trial, Blood 128 (22) (2016) 787-787.
[15] D. Rea, et al., Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study, Blood 129 (7) (2017) 846–854.
[16] J. Richter, et al., Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J. Clin. Oncol. 32 (25) (2014) 2821–2823.
[17] M.G.P.B. Berger, C. Oris, S. Saugues, P. Cony-Makhoul, M. Gardembas, L. Legros, M. Escoffre-Barbe, F.E. Nicolini, P. Rousselot, D. Rea, J. Guilhot, M. Zénut, A. Guerci, S. Giraudier, F.X. Mahon, Osteoarticular pain after discontinuation of Tyrosine Kinase Inhibitors (TKI): a French cohort, 57th ASH Annual Meeting and Exposition (2015) Abstract found here https://ash.confex.com/ash/2015/webprogram/Paper83688.html.
[18] P. Rousselot, et al., Reply to J. Richter et al, J. Clin. Oncol. 32 (25) (2014) 2823–2825.
[19] M. Ceko, et al., Inhibition of c-Kit signaling is associated with reduced heat and cold pain sensitivity in humans, Pain 155 (7) (2014) 1222–1228.
[20] D. Ramanujam, et al., Dramatic resolution of respiratory symptoms with imatinib mesylate in patients with chronic myeloid leukemia presenting with lower airway symptoms resembling asthma, Leuk. Lymphoma 50 (10) (2009) 1721–1722.
[21] M. Breccia, G. Alimena, The metabolic consequences of imatinib mesylate: Changes on glucose, lypidic and bone metabolism, Leuk. Res. 33 (7) (2009) 871–875.

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