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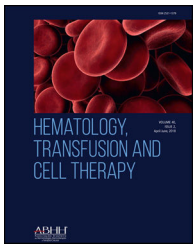

Case Report

A case of neurocognitive deficit strongly related to dasatinib therapy

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Introduction

Dasatinib is a potent BCR/ABL tyrosine kinase inhibitor (TKI) that has been become widely used in the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph-positive CML) due to its high efficacy and tolerability.[1–3] Treatment-naïve patients receiving dasatinib achieved higher complete cytogenetic response at 12 months, compared to patients receiving imatinib (77% vs 66%, respectively), which advocates for its use as a first-line agent in CML.[2] The most common nonhematologic events reported with dasatinib were fluid retention, diarrhea, headache, rash, and musculoskeletal pain.[1,2] The 5-years follow-up of the phase III DASISION trial comparing dasatinib to imatinib reported similar adverse events to those described in earlier investigations, and no neurocognitive changes were reported in either treatment arm.[2] However, memory impairment was reported in a few other investigations in a small number of patients receiving dasatinib.[4–6]

Case report

A 34-year-old high-functioning licensed process engineer presented to our clinic with leukocytosis and was diagnosed with Ph-positive CML. He was started on standard dose dasatinib, which he initially tolerated well, with mild fatigue as his main complaint. At 38 months into his treatment, he started reporting memory decline, difficulty in concentrating and distractibility that were slowly progressing over a 6-month period. He stated that the onset was gradual, but that the symptoms began interfering with his day-to-day activities and his job. He denied having any previous cognitive difficulties and there were no neurological disorders, or known depression, anxiety or mental health issues in his family. Neurocognitive testing revealed deficits in verbal memory retrieval, right-hand fine motor speed, verbal fluency and confrontational naming. Magnetic resonance imaging (MRI) of his brain was unremarkable. The polymerase Chain Reaction (PCR) for BCR/ABL1 showed that he was still in major

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molecular response (MMR). Blood tests showed mild cytopenia with normal electrolytes, thyroid stimulating hormone (TSH), vitamin B12, and kidney and liver indices. After all possible medical causes were ruled out, his symptoms were attributed to dasatinib and the treatment was stopped. Within 3 days, the patient reported increased energy and within 2 weeks a better focus. At 4 weeks he was started on bosutinib and at 6 weeks he had a repeat neurocognitive evaluation that showed robust and dramatic improvement in verbal memory (CVLT-II Short-Delay Free Recall, +1.5 SDs and CVLT-II Long-Delay Free Recall, +2.5 SDs) and learning (Learning Slope Trials 1–5, +3.0 SDs); significant improvements in phonemic fluency (+1.5 SDs), semantic fluency (+1.7SDs), complex concentration, mental flexibility and multitasking (TMT-B, +0.9 SD), and; right-hand fine motor speed (Finger Tapping + 0.8 SDs). He now continues to tolerate bosutinib well, with no recurrence of any neurocognitive symptoms after more than 1 year of therapy.

Discussion

In this report we describe a robust cause–effect relationship between the use of dasatinib and the development of neurocognitive impairment. We performed a search on pubmed using the key word "dasatinib" and filtering solely for case reports found only two case reports that have described neurological (reversible demyelinating peripheral polyneuropathy)[7] or psychiatric adverse events (agitation)[8] associated with the use of dasatinib. In addition to memory loss, our patient's symptoms were strongly lateralized to the left cerebral hemisphere and implicated focal dysfunction in anterior regions in particular. Although memory loss was reported in small retrospective studies of patients on dasatinib, it is hard to establish causality, due to the nature and limitations of these studies.[4–6] One study observing 99 patients with no history of neuropsychiatric disorders found that 19% of the patients were susceptible to memory changes, on a standard dasatinib dose, after a median of 41 months. Of these, 21% reported grade 3 changes with improvement or resolution of their symptoms after treatment interruption or dose modification.[5] Another study focusing on TKI-related toxicities reported difficulty in remembering among the top five most severe symptoms reported by patients.[4] Since some cognitive impairment is often expected in patients receiving cancer therapy, frequently referred to as "chemo brain", mild memory symptoms may go underreported in large clinical trials.[9] Higher functioning individuals, such as this patient, are more likely to become aware of, and frustrated by, these deficits.

The neurocognitive effects of dasatinib could be due to its higher penetration across the blood-brain barrier, when compared to other TKIs.[10] However, these changes appear to be progressive but reversible when therapy is discontinued. Dasatinib is a dual Src/Abl inhibitor.[11] In murine microglia cell lines and in murine models, dasatinib was found to inhibit Src kinase that is one of the multiple non-receptor tyrosine kinases involved in the activation of microglia.[12] Although this effect is believed to be beneficial in a brain with Alzheimer's disease, through the reduction of the amyloid beta induced microgliosis, its effect on a normal brain remains unknown.[12] Additionally, non-receptor Src family tyrosine kinases are known to play a crucial role in neuronal development[13] and synaptic plasticity.[14] On the other hand, the Abl kinase is known to regulate neuronal activity, mainly through cell death regulation,[15] parkin phosphorylation[16] and tau phosphorylation.[17] Our hypothesis is that the symptoms observed in our patient were possibly due to a reversible dysregulation in one or more of the above-mentioned regulatory mechanisms. Rapid improvement back to the baseline was seen in our patient after the cessation of the treatment. Furthermore, transitioning to a different second-generation tyrosine kinase inhibitor did not elicit a recurrence in his symptoms. Although rare, this complication can severely impact the life of patients on long-term dasatinib treatment. Understanding and recognizing this side effect is crucial, as these changes are rapidly reversible with the timely cessation of the treatment, and appear not to occur with other TKIs.

Conflicts of interest

The authors declare no conflicts of interest.

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