CASE REPORT

Severe agitation in depression precipitated by dasatinib

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SUMMARY

We describe a case of a man with chronic myeloid leukaemia who achieved remission through dasatinib therapy after being unable to tolerate several tyrosine kinase inhibitor (TKI) regimens due to severe physical side effects. However, this coincided with the onset of distressing agitation, insomnia and motor restlessness leading him to take a large zopiclone overdose. Start of appropriate therapy with a clonazepam, venlafaxine and mirtazapine combination led to a rapid improvement in symptomatology. We discuss the differential diagnosis and review the literature of neuropsychiatric complications of TKIs. This case serves as an illustrative reminder that in cases of complicated agitation referral to specialist mental health teams for rational psychopharmacological management is advised.

BACKGROUND

The development of tyrosine kinase inhibitors (TKIs) has been unequivocally associated with positive outcomes in cases of chronic myeloid leukaemia, with survival rates of 88–95% reported at 6 years.[1] However, in a subset of patients they are noted to be associated with poorer mental health outcomes, in particular causing depression and insomnia (1–10%) and, less commonly, anxiety (0.1–1%) in the original Phase II and III trials (n=2182).[2] However, very little work has been undertaken to follow this up and consequently there is a concern that psychiatric complications are under-recognised in these patients. Furthermore, it is not known whether these medications can worsen the course of mood disorders in those with a history of recurrent depression. We report a clinical presentation of severe agitation with commencement of TKI therapy in a man with a likely previously latent depressive disorder. We discuss in depth the differential diagnosis and rapid response to effective treatment. This case is important to illustrate this particular adverse effect of TKIs, to illustrate treatment options and to advise psychiatric referral which may be life changing in such patients.

CASE PRESENTATION

A 62-year-old driving instructor was referred to the psychiatrists because of insomnia, low mood and feelings of inner restlessness over the course of a year after starting dasatinib. He was eventually unable to tolerate the agitation and had overdosed on 3 months supply of zopiclone 7.5 mg tablets in an attempt to end his suffering. After having been stabilised medically, he had not wished to continue with an inpatient psychiatric admission and the community mental health team was asked to follow-up.

On presentation his main concern had been regarding the marked lack of sleep that had diminished to 2–3 h a night since starting the medication. He would find himself restless, on edge and fidgety. He found the whole process exhausting and draining. He was experiencing a low mood; however, he was clear that it was the agitation he found more debilitating. There was no recurrent suicidal ideation and he was clear that the act had been a means of escape from the desperate state of his restlessness rather than resultant to the low mood. There were no feelings of guilt or loss of self-esteem. He was still able to enjoy activities such as attending the theatre, although he had found himself unable to work in his current condition.

Over the past 5 years he had been diagnosed with Philadelphia positive chronic myeloid leukaemia. Over this period he had tried a number of protein kinase inhibitors and suffered from various distressing side effects: (1) with imatinib (gleevec) —he had noted blistering and his skin peeling off (exfoliative dermatitis); (2) dasatinib at higher doses (100 mg/day) had resulted in a pleural effusion and (3) on nilotonib he had experienced painful stomach cramps and lymph gland swelling with hallucinations. Owing to this condition, in 2011 he was treated with high dose steroids over a weekend, which caused a hypomanic episode, and he was noted to be 'speaking at twice the speed'. At the time of current referral he was (4) stabilised on a lower dose of dastanib, 25 mg/day on alternate weeks for the last year. His white cell count had been well controlled with this. However, since commencing the dasatinib he had been experiencing a marked deterioration in mental state, eventually leading to the current presentation.

The general practitioner (GP) had started venlafaxine 150 mg with partial success. A switch to citalopram was trialled with withdrawal of venlafaxine; this, however, precipitated a marked deterioration in symptoms. Subsequent restart over the past 3 months of venlafaxine and titration up to 225 mg had no effect, leading up to the current overdose. Zopiclone and, more recently, promethazine had been started in order to alleviate the insomnia, with little effect. At the time of presentation, the patient was taking: (1) dastanib 25 mg once daily (every other week), (2) amiloride (every other day) (3) venlafaxine 225 mg once daily (4) zopiclone 7.5 mg once nightly and (5) promethazine 50 mg once nightly.

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History revealed that at the age of 30 he had experienced an episode of low mood and tried to kill himself with fumes from the exhaust from his car. He had experienced a few other periods of low mood over the next 30 years but had never been diagnosed with depression or required medication. There had been no other severe episodes. His first diagnosis of depression was made after starting TKIs 2 years ago and he had first started antidepressants at this time. Initially, his distress had been attributed to the severe physical side effects he had been experiencing due to the medication as described above; however, on this occasion the distress was evident in the absence of physical side effects.

INVESTIGATIONS

Other medical reasons had been excluded as a cause for his current presentation. Full blood count, urea and electrolytes, liver function tests and thyroid function tests were normal. He had recent unremarkable CT and MRI head scans to rule out neurological causes. ECG revealed a sinus rhythm with a QTc of 400 ms.

Mental state examination revealed a casually dressed man who was notably anxious. He had difficulty sitting still without fidgeting, and was constantly crossing and uncrossing his legs and fidgeting with his hands. There was a quiver to his voice with no paucity or pressure of speech. He came across as predominantly anxious and agitated. He explained that he would feel like this most days with some improvement towards the latter part of the day. Sleep was particularly disturbed and he felt exhausted throughout the day. He was able to enjoy activities. There was no evidence of psychotic symptoms or suicidal ideation. However, he later admitted that he could not guarantee that he would not overdose again given his agitation and this remained a concern.

DIFFERENTIAL DIAGNOSIS

In our patient alternate explanations were considered for the presentation:

1. The agitation could have been the result of a severe relapse of a mood disorder independent of TKI use. However, the marked deterioration with start of the episode at the same time as starting a medication known to cause neuropsychiatric sequalae, pointed away from this. It is notable that prior to TKI start he had not had a severe depressive episode for the past 30 years. Since TKI use he had developed dramatic mood disturbance on all TKI medications as noted by patient, partner and GP.
2. His condition may have been a relapse of the previously latent depressive disorder due to TKI use. The clinical history strongly suggests periods of restlessness and dysphoria whenever TKI use was started. Although this had been initially masked by physical distress it was now clear this was related to the TKI use independent of physical health symptoms. The Naranjo probability scores[3] for the various implicated medications can be seen in table 1, showing TKI use as the likely candidate for the agitation.

The diagnosis of 'agitated depression' is subsumed under severe non-psychotic depression in both International Statistical Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (ICD-10 F33.2, DSM-IV-TR 296.33). The agitation would eventually make good response to combination antidepressant therapy. Other features in support of this are the low mood, the fatigability, marked sleep disturbance as well as the history. However, it is also worth considering that the anhedonia was not complete; and the suicidal act in this instance was not due to low mood but rather an inability to tolerate the restlessness. This may indicate either a partially treated depressive picture at presentation, as the patient was on venlafaxine at this time, or a predominantly agitated picture of the current mood episode.

3. An alternate diagnosis of dasatinib induced akathisia (ICD-10 G25.71, DSM-IV-TR 333.99) was considered. The coding systems noting that it can be difficult to clinically distinguish between states (2) and (3). A chronic akathisic picture remains over 3 months from commencement of medication and presents with dysphoric features and inner restlessness, as our patient demonstrated.[4] The 'gold standard' test to prove this

Table 1 Naranjo Probability Scoring for medications associated with agitation

	TKIs	Venlafaxine	Promethazine
Are there previous conclusive reports on this reaction?	Yes (1)	Yes (1)	Yes (1)
Did the adverse events appear after the suspected drug was given?	Yes (1)	No (0)	No (0)
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes (1)	No (0)	No (0)
Did the adverse reaction appear when the drug was readministered?	Yes (2)	No (−1)	Not done (0)
Are there alternative causes that could have caused the reaction?	Yes (−1)	Yes (−1)	Yes (−1)
Did the reaction reappear when a placebo was given?	Not done (0)	Not done (0)	Not done (0)
Was the drug detected in any body fluid in toxic concentrations?	Not done (0)	Not done (0)	Not done (0)
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Do not know (0)	No (0)	No (0)
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes (1)	No (0)	No (0)
Was the adverse event confirmed by any objective evidence?	No (0)	No (0)	No (0)
Totals	5	−1	0
Scoring of adverse drug reaction			
≥9=definite 5–8=probable 1–4=possible 0=doubtful	*Probable adverse drug reaction*	*Doubtful adverse drug reaction*	*Doubtful adverse drug reaction*

TKI, tyrosine kinase inhibitor.

would have been to stop dasatinib and rechallenge but this was not possible due to the life-preserving nature of the drug.

However, given the history of a dormant undiagnosed depression and the response to antidepressant therapy, new onset akathisia is perhaps less likely.

4. An alternate possibility to be considered was the combination of psychotropic medications leading to the agitation. However, although the fact that venlafaxine and promethazine cause akathisia has been recognised, in this case symptom-onset preceded, by several months, the start of venlafaxine and promethazine. Dasatinib and amiloride were the only active medications at the start of symptoms. Venlafaxine also appeared to ameliorate symptoms, which pointed away from this as a causal factor. Naranjo probability scores are correspondingly low (table 1).

TREATMENT

Venlafaxine was reduced to 150 mg, as higher doses can be associated with exacerbating agitation. Mirtazapine at a low dose (15 mg) was started as adjunctive treatment and to help with insomnia. A short course of long-acting benzodiazepines, Clonazepam 1 mg three times a day was prescribed as an anxiolytic. Given the urgency of the situation, the patient was followed up on a weekly basis initially.

OUTCOME AND FOLLOW-UP

By the next clinic appointment, the patient had markedly settled, stating that improvement had been noticeable within 3–4 days. He was now sleeping 5–6 h a night, he had found that the inner tension had gone and he had not had any further thoughts of not wanting to go on. The marked improvement of his symptoms was confirmed by his partner. The only side effect he was experiencing from the medication he was started on was a dry mouth. Over the next month he was weaned off the clonazepam, zopiclone and promethazine with close community mental health team monitoring and no deterioration in symptoms. Consequently, his medication regime has been stabilised to: (1) dastinib 25 mg once daily (every other week), (2) amiloride (every other day) (3) venlafaxine 150 mg once daily and (4) mirtazapine 15 mg once nightly. The weaning off clonazepam and successful treatment with combination antidepressants further suggests that the restlessness had been due to drug-induced depression rather than akathisia.

DISCUSSION

A recent case control study of 62 patients taking TKIs (mean 4 years) compared with 62 non-cancer age and sex-matched controls showed significantly more depression and poorer quality of life outcomes in patients taking TKIs.[5] The presentation of severe depression with features of agitation has previously only been reported in one small case series of seven patients treated on imatinib or dasatinib in the literature. In four of these patients, response was only achieved via cessation of the TKI, in one patient outcome was not specified and two patients continued on TKIs with combination antidepressant therapy.[6] In none of these was a history of depressive illness reported. Consequently, this case report is the first to suggest the unmasking of a previously latent recurrent depressive disorder from TKI therapy.

In this case, stopping dasatinib was contraindicated by the life prolonging nature of the causative agent and the side effect profile he had experienced by other agents. National Institute for Health and Care Excellence (NICE) guidance advises a possible strategy of combination therapy with mirtazapine in the case of treatment non-response to monotherapy and limiting benzodiazepine use to short-term treatment only.[7] The rapid response seen in this case is likely due to the clonazepam, a highly effective and rapidly acting drug for anxiety and agitation. Mirtazapine has also been noted to have a more rapid onset of action than other antidepressants, and is an effective agent for insomnia.[8] It is likely that adequate antidepressant response of the venlafaxine–mirtazapine combination sustained the improvement when clonazepam was withdrawn. This combination targets both presynaptic receptors via mirtazapine (α 2 antagonist) and postsynaptic receptors via venlafaxine (combined serotonin and norepinephrine reuptake inhibitor) and has been used with success in persistent depression.[9]

Although clinically it would have perhaps been more satisfying to change one medication at a time to more accurately determine the agent responsible for therapeutic response, in this case the urgency of presentation necessitated a multipronged strategy. Consequently, in such situations, rational psychopharmacological prescribing under a specialist mental health team is a prerequisite to optimal patient care.

Learning points

- Tyrosine kinase inhibitors have remarkably improved outcomes for chronic myeloid leukaemia in the last decade.
- In a subset of patients they can precipitate severe depressive and anxiety symptoms with features of restlessness.
- Attempted or completed suicide is a risk if left untreated.
- In such situations referral to a mental health team for specialist care is advised.

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Unexpected outcome (positive or negative) including adverse drug reactions