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Possible modulation of concurrent Parkinson's disease in the management of metastatic GIST: a review of two cases

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Abstract

Imatinib, a tyrosine kinase inhibitor, is the mainstay of treatment for resected high-risk (adjuvant and metastatic) gastrointestinal stromal tumour (GIST) – a rare form of sarcoma. There has been recent research into the neuroprotective role and modulation of dopaminergic neurones by imatinib through the abl pathway in Parkinson's disease (PD). We describe two patients from a single cancer centre with concurrent diagnoses of PD and metastatic GIST receiving imatinib and standard PD management. The cases highlight a potential reduction in PD progression using Unified Parkinson's Disease Rating Scale. Further research into repurposing of imatinib for PD may provide additional management options for this neurodegenerative illness.

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Introduction

Sarcomas represent less than 1% of all diagnosed cancers and comprise up to 100 different diagnostic categories. Of these categories gastrointestinal stromal tumours (GISTs) are the most common, with an incidence of approximately 14.5 per million people per year as stated in the Swedish tumour registry, and a range of 10–15 per million per year as stated in a recent systematic reviewed published in 2016.[1,2] The management of metastatic and high-risk surgically resected GISTs is focused on the use of imatinib, a tyrosine kinase inhibitor, which has also revolutionised the management of chronic myeloid leukaemia via the abl pathway.[3] It has been shown that GISTs do not respond to conventional cytotoxic chemotherapy.[1]

Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterised by a number of motor and non-motor features due to dopaminergic neuronal loss.[4] Meta-analyses have shown that PD prevalence is increasing worldwide with 1,903 per 100,000 being affected in those over 80 years old. In addition, it has been shown that there is a geographic variation in prevalence. Prevalence is higher in westernised countries, with 1,601 per 100,000 affected in North America, Europe and Australia compared to 646 per 100,000 in Asia.[5]

PD has the potential to cause significant impact on a patient's function, and pharmacological management is centred on dopamine modulation. There are three cardinal features of PD: bradykinesia, resting tremor and rigidity. A number of rating scales have been developed to objectify PD severity, of which the Unified Parkinson's Disease Rating Scale (UPDRS) is the most established.[4,6] A revision of the UPDRS by the Movement Disorder Society (MDS-UPDRS) was published in 2008.[7] The MDS-UPDRS includes four domains: 1, non-motor experiences of daily living; 2, motor experiences of daily living; 3, motor examination; and 4, motor complications. We utilised patients ranked on both scores and focused on the third domain (objective motor neurological examination) that we denote as 'UPDRS 3' with R = right side, A = axial features and L = left side.

When assessing PD medication it can often be difficult to make a comparison between patients owing to a number of different types of dopaminergic medication and variations in equivalence. A systematic review by Tomlinson et al. provides a standard formula that produces a levodopa equivalent daily dose (LEDD) expressed in milligrams per day. This allows for comparison of dopaminergic medication across patients and studies.[8]

We describe two male patients with a concurrent diagnosis of PD and metastatic GIST managed with imatinib and standard therapy for PD. All available UPDRS scores and LEDDs from both electronic files and paper case notes were collated. There is a potential observation that expected deterioration in PD may have been slowed by their concurrent management with imatinib.

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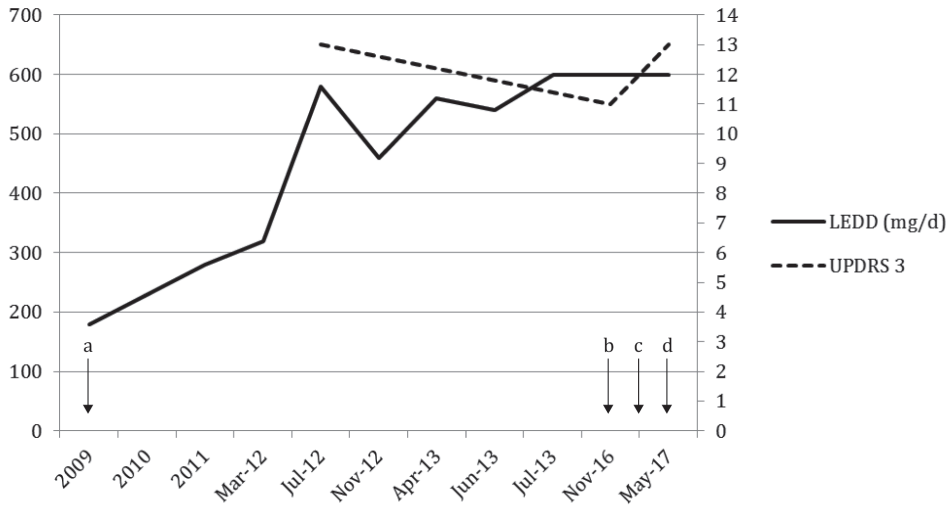

Figure 1 Change in Unified Parkinson's Disease Rating Scale 3 (UPDRS 3; left axis) and levodopa equivalent daily dose (LEDD; right axis) with time. a = Parkinson's disease diagnosis; b = metastatic gastrointestinal stromal tumour diagnosis; c = initiation of imatinib; d = most recent neurology clinic follow up

Case one

A 68-year-old male with PD diagnosed in 2009, initially presented with shuffling gait and poor writing. In 2015 the patient had a UPDRS 3 of 13/132 (bradykinesia = 8, rigidity = 5). On examination he had decreased blinking, slowed left finger taps, hand movements and arm rotation, bilateral reduced arm swing and slight stooped posture. LEDD at that time was 180. He was commenced on imatinib in January 2017 for metastatic GIST (gastric primary with liver metastasis and a solitary peritoneal nodule), which was diagnosed in December 2016 where UPDRS 3 was 11/132 (R4/44, A2/44, L5/44). The introduction of imatinib led to a partial response and symptomatic improvement, with reduction in abdominal pain. Currently, as of May 2017, he is being managed with 25 mg carbidopa/100 mg levodopa one tablet six-times daily – equating to a LEDD of 600. On examination at his last clinic appointment he had general slowed movements and mild rigidity with the option to reduce his Sinemet® dose owing to dyskinesia. Both dopaminergic treatment and complete UPDRS 3 scores are displayed chronologically in Figure 1.

Case two

A 72-year-old male was diagnosed and started treatment for PD (LEDD 180) in 2003, and subsequently underwent a gastric resection for a high-risk GIST in 2009. On follow-up imaging in 2014 he had multiple liver lesions, which on biopsy were shown to be metastatic GISTs. At this point his UPDRS 3 was 14/132 (R5/44, A4/44, L5/44). Subsequently the patient received imatinib, where his UPDRS 3 was 18/132 (R3/44, A8/44, L7/44) in November 2014 with LEDD 1,110 for 36 months leading to stable disease on CT imaging. He reports that imatinib has improved his PD and remains well with a WHO performance status of 1. UPDRS 3 in June 2017 was 19/132 (bradykinesia = 13; rigidity = 2; tremor = 4; postural instability = 0). Examination showed slightly affected speech, mildly reduced facial expression with reduced blinking, bilaterally slowed finger tapping, hand movements, pronation/supination, reduced right-sided toe tapping and arising from chair, reduced right arm swing with stooped posture and bilateral tremor. As of January 2018, dopaminergic therapy equated to LEDD 1,425. Both dopaminergic treatment and complete UPDRS 3 scores are displayed chronologically in Figure 2.

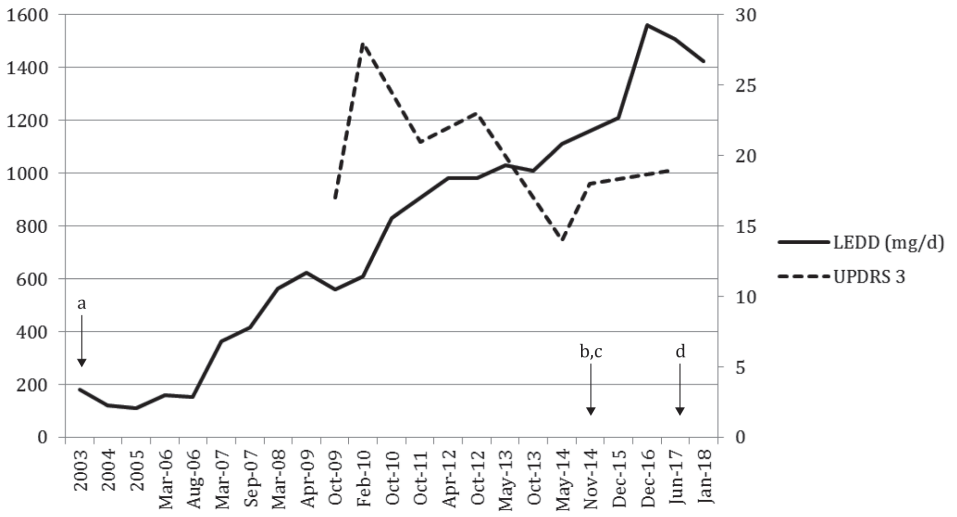

Figure 2 Change in Unified Parkinson's Disease Rating Scale 3 (UPDRS 3; left axis) and levodopa equivalent daily dose (LEDD; right axis) with time. a = Parkinson's disease diagnosis; b = metastatic gastrointestinal stromal tumour diagnosis; c = initiation of imatinib; d = most recent neurology clinic follow up

Discussion

These two cases raise the possibility that imatinib may modulate the severity of PD. Both patients report their PD symptoms being less troublesome despite receiving additional treatment for their comorbid tumours, which is unusual considering that most PD patients with intercurrent illness report subjective worsening.[9] Some corroboration of this clinical impression comes from the routinely obtained UPDRS 3 scores, which show stability or improvement since the introduction of imatinib.

The pathology of PD is well known. This involves the loss of dopaminergic neurones in the substantia nigra and development of Lewy bodies in multiple other brain regions.[10] It is believed that the majority of cases are caused by interplay of genetic and environmental factors.

Mutations in *PRKN* gene encoding for Parkin, an ubiquitin E3 ligase involved in the degradation of misfolded proteins and mitochondrial function, is the most common cause of autosomal recessive PD.[11,12] However, it has recently been shown that Parkin may play a role in sporadic PD as it is inactivated owing to nitrosative stress (as a result of reactive nitrogen species), dopaminergic stress and oxidative stress: key pathophysiological processes in sporadic PD.[12]

A study from 2010 showed that tyrosine kinase c–abl phosphorylation of Parkin, which is activated during dopaminergic stress as shown in post-mortem studies, inhibited Parkin's ligase and protective function. Therefore, c-abl inhibition may be a neuroprotective strategy in the management of PD.[13] Imatinib, the drug of choice for high-risk adjuvant (surgically resected) GIST, has activity against a number of kinases, but of importance in this context, abl.[14,15]

It is difficult to draw definite conclusions from two cases regarding progression, but we can benchmark our observations against an average increase in UPDRS by 1.2 points per year in a large cohort study.[16] These findings are therefore preliminary, but suggest that observational data on a wider scale, including other diagnoses in which this drug class is used, would be worthwhile. Future work could be carried out with inclusion of this cancer centre's chronic myeloid leukaemia/PD cohort to increase sample size and clarify the correlation between UPDRS, LEDD and tyrosine kinase therapy.

There are a number of additional limitations that need to be considered. One is the use of dopaminergic medicines and the frequency at which PD medication is changed. In an attempt to standardise this often difficult area, we used LEDD as described above.

The use of UPDRS 3 should objectify patients' symptomatology; however, there is the possibility that external factors may have influenced clinical examination. We used the UPDRS 3 score, which relates to specialist neurological examination and not the more subjective UPDRS domains, such as patients' experiences of daily living. One can make the assumption that, in particular, the non-motor experiences of daily living (UPDRS 1), which include cognitive impairment, depressed mood, anxiety and apathy, may be influenced by the diagnosis of metastatic cancer.[6] We used all available UPDRS 3 scores from both electronic notes and paper case notes since PD diagnosis. The use of UPDRS has become more widely used in recent years, which allows for more accurate observations compared to those years nearer PD diagnosis.

Clinical trials in the USA are now in the recruiting phase to assess the impact of another tyrosine kinase inhibitor, nilotinib, and it will be interesting to see their results.[17]

Conclusion

Although we did not aim to prove the benefits of imatinib on PD progression, it does provide observational data that suggests stability or improvement in PD severity related to imatinib therapy. This is consistent with preclinical observations.

Several learning points have been identified:

- Phosphorylation of Parkin has a detrimental effect on neuroprotection in PD.
- There is possible modulation of PD using a tyrosine kinase inhibitor, which may help stabilise patients' symptomatology.
- Identification of pathways in rarer diseases may allow for repurposing of medication across medical specialties.

Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patients for publication of this paper, including accompanying images.

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