BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03893.x

Reversible posterior leucoencephalopathy syndrome in an elderly male on sunitinib therapy

Biswa M. Padhy, Saravana P. Shanmugam, Yogendra K. Gupta & Aman Goyal

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

Correspondence
Dr Biswa Mohan Padhy, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi 110029, India.
Tel.: +91 011 26593282
Fax: +91 011 26588641
E-mail: drbisu7@gmail.com

Keywords
causality assessment, leucoencephalopathy, sunitinib, vascular endothelial growth factor

Received
9 November 2010

Accepted
16 December 2010

Accepted Article
30 December 2010

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Agents inhibiting vascular endothelial growth factor can lead to development of reversible posterior leucoencephalopathy syndrome (RPLS).
- Few cases of sunitinib-induced RPLS have been reported previously.

WHAT THIS STUDY ADDS

- A case of sunitinib-induced RPLS in an elderly man is described in this study.
- Elevated blood pressure at presentation occurs in most cases of sunitinib-induced RPLS.

AIMS

Reversible posterior leucoencephalopathy syndrome (RPLS) has been reported following the use of anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab, sorafinib and sunitinib. In this report we present a case of RPLS that occurred in an elderly male on sunitinib therapy.

METHODS

Other case reports of sunitinib-induced RPLS were reviewed and causality assessment was carried out using the World Health Organization-Uppsala Monitoring Centre criteria and the Naranjo algorithm.

RESULTS

Only a few cases of sunitinib-induced RPLS had been reported previously and elevated blood pressure at presentation was common in most of the patients. Our case was clinically similar to the earlier reports and the adverse reaction had a 'probable' relationship with sunitinib intake.

CONCLUSIONS

Physicians should monitor and manage elevated blood pressure in patients with sunitinib-induced RPLS.

Introduction

Sunitinib is an oral, multitargeted tyrosine kinase inhibitor that inhibits the vascular endothelial growth factor (VEGF) receptor and platelet-derived growth factor receptor. The drug received US FDA approval in 2006 for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumours. Subsequently, in 2007, it was approved in India for metastatic RCC and has become a reference standard of care for the treatment of advanced stages of this malignancy [1]. We report a case of reversible posterior leucoencephalopathy syndrome (RPLS), occurring after initiation of sunitinib therapy for metastatic RCC.

Case report

A 65-year-old man presented to the emergency department following an episode of generalized tonic-clonic

seizures and vision loss. Two months previously he was diagnosed with RCC left kidney, with osseous metastases and had undergone cytoreductive nephrectomy. Ten days prior to presentation, the patient had been prescribed sunitinib, 50 mg day^{-1} for 4 weeks. On the eighth day of therapy, he developed headache, dizziness and weakness in both upper limbs. He also developed painless bilateral diminution in vision and had an episode of generalized tonic-clonic seizures. The patient had no history of concomitant medications (except one tablet of paracetamol 650 mg for headache), addiction or allergy to food or other drugs. He had no history of head injury, epilepsy or hypertension and there was no family history of neurological or psychiatric disorders.

The patient was afebrile, visual acuity was reduced to 6/36 bilaterally but pupillary reflexes were preserved and the fundoscopic examination was normal. The neurological examinations revealed loss of power in both arms and exaggerated deep tendon reflexes. The patient's blood pressure was elevated at the time of presentation (160/100 mmHg). Cerebrospinal fluid evaluation, complete blood count and coagulation profile were normal and other laboratory tests did not suggest any electrolyte imbalance or abnormality in liver function. Serum creatinine was 1.9 mg dl^{-1}, consistent with previous results at the time of surgery. An electroencephalogram carried out on the day of presentation was normal. A T2-weighted magnetic resonance imaging (MRI) of the brain demonstrated bilateral occipital and parietal high intensity lesions in the white matter, following which a diagnosis of RPLS was made. There was no evidence of tumour metastasis in the brain. The patient was admitted, sunitinib was withdrawn and nifedipine was started to control the elevated blood pressure. Two days after discontinuing sunitinib, the blood pressure was controlled and he reported considerable relief from headaches. However, there was only marginal improvement in visual acuity. On the tenth day, there was complete absence of headaches and visual acuity had partially recovered. A repeat MRI of the brain showed significant resolution of the lesions. The patient was kept under further observation for 1 week and discharged after complete recovery from vision loss. There was no seizure episode during the entire duration of hospitalization.

In view of the serious nature of the adverse drug reaction (ADR), re-challenge was not carried out. Causality assessment carried out using the World Health Organization-Uppsala Monitoring Centre criteria revealed that the reaction had 'probable' relationship with sunitinib intake. The association was also evaluated using the Naranjo algorithm and a score of 5 indicated a 'probable' relationship [2]. The ADR was reported to the national pharmacovigilance centre under the National Pharmacovigliance Programme, India.

Table 1

Cases of reversible posterior leucoencephalopathy syndrome after sunitinib therapy

Case #	Age (years)/ Gender	Indication for sunitinib therapy	Onset after starting sunitinib	Clinical presentation	Blood pressure (mmHg) at presentation	Management	Recovery after sunitinib discontinuation
Case 1 [3]	54/F	Imatinib-resistant gastrointestinal stromal cell tumour	8 months	Vision loss, generalized seizures, thromocytopenia	210/110 (previously had suboptimally controlled hypertension)	Sunitinib discontinuation, anticonvulsants, antihypertensives, fresh frozen plasma	Complete recovery in 10 days
Case 2 [4]	70/F	RCC, bone metastases	2 weeks	Headache, vision loss, partial seizures	170/100 (previous condition not specified)	Sunitinib discontinuation, anticonvulsants, antihypertensives	Complete recovery in few days
Case 3 [5]	81/F	RCC, liver and lung metastases	5 months	Diziness, unconsciousness, Confusion	130/74 (had well controlled hypertension)	Sunitinib discontinuation	Complete recovery in 1 month
Case 4 [6]	39/F	RCC, ovarian metastases	1 week	Headache, confusion, generalized seizures, hemiplegia, visual disturbances	160/102 (previously normotensive)	Sunitinib discontinuation, anticonvulsants, antihypertensives	Complete recovery in 2 weeks
Case 5 [7]	48/F	RCC, retroperitoneal lymph node metastases	1 week	Headache, generalized seizures, unsteadiness	190/130 (previously had well controlled hypertension)	Sunitinib discontinuation	Complete recovery in 3 weeks
Present case	65/M	RCC, vertebral metastases	8 days	Headache, weakness in upper limbs, generalized seizures, visual loss	160/100 (previously normotensive)	Sunitinib discontinuation, antihypertensive	Complete recovery in 17 days

Discussion

The typical symptoms of RPLS are headache, seizures, visual abnormalities and altered mental status. The characteristic radiological findings are bilateral grey and white matter oedematous lesions in the posterior regions of the cerebral hemispheres. Its pathogenesis involves disruption of cerebral vascular endothelial cells and impaired cerebrovascular autoregulation leading to oedema secondary to conditions such as hypertension, eclampsia, systemic lupus erythematosus and thrombotic thrombocytopenic purpura [3, 4]. Drugs that have been associated with RPLS include immunosuppressive agents and cytotoxic drugs like cyclosporin A, tacrolimus, cisplatin, cytarabine and L-asparaginase [4]. Recently, the syndrome has also been reported following the use of anti-VEGF therapies like bevacizumab and sorafinib [4, 5]. However, there are very few reports of RPLS following use of sunitinib and the underlying mechanisms are largely unknown [3–7]. The prescribing information of sunitinib also lists RPLS as a rare ADR [8]. The clinical and MRI features in the reported cases were similar to our case, except that time to onset of RPLS was variable (1 week to 8 months) and that one case had not developed hypertension during sunitinib therapy (Table 1). It has been reported that nearly 47% of patients on sunitinib therapy develop hypertension which resolves within 1–2 weeks after discontinuing the drug [7]. In the present case, it is possible that endothelial dysfunction secondary to VEGF inhibition and sunitinib-induced hypertension along with pre-existing renal dysfunction could have culminated in the event. The absence of metastatic foci in the brain and rapid resolution of the clinical features and radiologic lesions after stopping the drug corroborates with this hypothesis. This case reiterates that, although rare, there is a possibility of development of RPLS with sunitinib use. The condition could be potentially life-threatening or become irreversible if untreated [7]. Hence, physicians should closely monitor and manage elevated blood pressure in patients developing RPLS during sunitinib therapy.

Competing Interests

There are no competing interests to declare.

REFERENCES

1 Jain R, Mathew P, Wood CG, Tannir NM. Sunitinib-induced acute hemolysis without hypertension: a case report. Clin Genitourin Cancer 2008; 6: 122–3.

2 Farcas A, Bojita M. Adverse drug reactions in clinical practice: a causality assessment of a case of drug-induced pancreatitis. J Gastrointestin Liver Dis 2009; 18: 353–8.

3 Kapiteijn E, Brand A, Kroep J, Gelderblom H. Sunitinib induced hypertension, thrombotic microangiopathy and reversible posterior leukencephalopathy syndrome. Ann Oncol 2007; 18: 1745–7.

4 Martín G, Bellido L, Cruz JJ. Reversible posterior leukoencephalopathy syndrome induced by sunitinib. J Clin Oncol 2007; 25: 3559.

5 Medioni J, Cojocarasu O, Banu E, Cassar-Queudeville A, Halimi P, Oudard S. Reversible encephalopathy syndrome secondary to sunitinib for metastatic renal cell carcinoma patient. Targ Oncol 2007; 2: 193–5.

6 Cumurciuc R, Martinez-Almoyna L, Henry C, Husson H, de Broucker T. Posterior reversible encephalopathy syndrome during sunitinib therapy. Rev Neurol (Paris) 2008; 164: 605–7.

7 Chen A, Agarwal N. Reversible posterior leucoencephalopathy syndrome associated with sunitinib. Intern Med J 2009; 39: 341–2.

8 Prescribing Information. Sutent® (sunitinib malate) oral capsules. Pfizer Inc. Available at http://www.pfizer.com/files/products/uspi_sutent.pdf (last accessed 5 November 2010).