Possible ifosfamide-induced panic attacks

Sir,

The anticancer drug ifosfamide is associated with 5-30% incidence of central nervous system toxicity.[1] Manifestations range from somnolence, confusion and agitation, through delusions, hallucinations and psychosis to even seizures and coma.[2,3] These neuropsychiatric complications are usually of acute onset and subside within 48-72 h, although persistent psychopathological symptoms, irreversible encephalopathy, and even neurotoxic deaths have been recorded.[2,3] Even though anxiety is known to be part of ifosfamide-induced neurotoxicity, panic attacks are yet to be documented. We report two cases of suspected ifosfamide-induced panic attacks.

Case 1: A 47-year-old man with arsenic-induced carcinoma of the hard palate and positive neck nodes was started on ifosfamide (2 g IV on Days 1 and 2; followed by 1 g IV on Day 3) and cisplatin (50 mg IV on Days 1, 2 and 3) combination chemotherapy. The first cycle was given between 04.11.2006 to 06.11.2006, the second between 02.12.2006 to 04.12.2006, and the patient discharged thereafter. Two weeks later, he presented in the outpatient department (OPD) with a seven-day history of multiple episodes of sudden onset palpitation, breathlessness, sweating, intense fear and sensation of ‘impending doom’. The episodes were unpredictable and lasted for 10-15 min each.

We witnessed one such episode during which, apart from tachycardia, vital signs were satisfactory. Systemic examination was also normal, except that the patient was highly anxious and sweating profusely. Panic attack was provisionally diagnosed and alprazolam 0.5 mg twice daily, atenolol 50 mg once daily and diazepam 5 mg at bedtime started. The attacks were controlled within a week but recurred on the third cycle (between 25.12.2006 to 27.12.2006). This time, investigations revealed normal blood glucose, thyroid status, ECG and echocardiography. The recurrent episode was controlled by the same medicines as earlier and these were continued during the last two cycles of chemotherapy. No further attacks occurred.

Case 2: A 32-year-old woman with maxillary antrum carcinoma received ifosfamide (2 g IV on Day 1 followed by 1 g IV on Day 2) and cisplatin (80 mg IV on Day 1) combination. On the morning after the first day of chemotherapy (23.07.2007), she complained of pounding heartbeat, breathlessness and a sensation of ‘impending doom’. On examination, pulse was 90 bpm and the patient anxious, trembling and sweating profusely. This episode resolved spontaneously in about 15 min. The second day’s chemotherapy was administered and the patient discharged next morning with advice to take alprazolam 0.5 mg at bedtime for three weeks and relevant laboratory workup. One week later she visited the OPD. Panic symptoms had not recurred and tests ruled out cardiac or endocrine pathology.

As per DSM IV criteria, ‘panic attack’ can be clinically diagnosed if there is a discrete period of intense fear in which four or more out of 13 listed symptoms develop abruptly and peak within 10 min. Our cases satisfied the criteria. Theensorium was clear during the witnessed attacks. As per US National Cancer Institute Common Terminology Criteria for Adverse Events Version 3, the severity of both cases qualifies as moderate (Grade 2) under the neurological mood alteration category. Interestingly, apart from the panic features, other neuropsychiatric symptoms (including hallucinations) were not reported at any point of time. Neither patient gave history of substance abuse, psychiatric illness or major stressful events in the recent past.

The events were ‘Probable/Likely’ with respect to ifosfamide as the causal drug by the World Health Organization-Uppsala Monitoring Centre criteria.[4] Although both subjects received ifosfamide-cisplatin combination, only ifosfamide is known to cause neuropsychiatric symptoms. Cisplatin neurotoxicity manifests as peripheral neuropathy, sensorineural deafness or optic neuritis but not as neuropsychiatric symptoms. Besides the anticancer drugs, both patients received mesna uroprotection (400 mg of mesna IV/g of ifosfamide) and premedication with dexamethasone (8 mg IV) and ondansetron (12 mg IV). These are also not likely to cause panic attacks. Neither subject received cranial irradiation therapy.

Ifosfamide neurotoxicity is known to exhibit some dose-dependence, although relatively lower doses of 3 g/m²/cycle have been reported to cause psychiatric symptoms including anxiety-depression and hallucinations.[2] Extrapyramidal toxicity has been reported at 5 g/m²/cycle[11] and visual and
auditory hallucinations at 15 g/m²/cycle or higher. However, conclusive evidence of dose-dependent neurotoxicity is lacking. In our patients, the panic symptoms occurred at doses of 3-5 g/cycle. Risk of ifosfamide neurotoxicity may increase with renal compromise. This too was not the case here.

Although the precise mechanism of ifosfamide neurotoxicity is unknown, chloroacetaldehyde (CAA), a metabolite, has been implicated. Chloroacetaldehyde is structurally related to acetaldehyde and chloral hydrate, both of which are neurotoxic. Differences in the metabolism of various oxazaphosphorines to CAA may explain the fact that ifosfamide shares the myelosuppressive and urotoxic potential of its parent compound cyclophosphamide but alone shows neurotoxic features. In a study measuring plasma concentration of CAA in six ifosfamide-treated children, the two who developed neurotoxic symptoms had higher levels than the rest. It is also possible that individual reactions to ifosfamide depend on inherited genetic polymorphisms, especially associated with the GSTP1 gene coding for glutathione S-transferases.

In conclusion, panic attacks may be the sole or first manifestation of ifosfamide-induced neurotoxicity and may occur at relatively low doses. Remaining alert to this possibility will allow the patient’s distress to be minimized rapidly.

References