Unexpected outcome (positive or negative) including adverse drug reactions

Vincristine-induced unilateral ptosis with serendipitous response to modafinil

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Here we describe a scenario of an atypical manifestation of vincristine-induced neurotoxicity, which responded serendipitously to modafinil. Atypical in that this patient had developed a uniocular ptosis, a rare manifestation of vincristine-induced neurotoxicity. The improvement in neurotoxicity after modafinil was started to alleviate morphine-induced sedation was quite noteworthy.

BACKGROUND

Although vincristine has a crucial and established role in treating many solid and haematological malignancies, its dose-limiting toxicity has been neurotoxicity, the incidence of which increases with an increase in cumulative dose. This neurotoxicity can be manifest as cranial, peripheral, autonomic and posterior pituitary disturbances.¹ Oculomotor involvement is uncommon, and, if at all present, it usually manifests bilaterally.

In our patient, the development of a uniocular ptosis and ophthalmoplegia (figure 1) had initially led us to suspect an intraocular or intracranial metastasis, which were subsequently ruled out by imaging.

Coincidentally, the patient had been on morphine for severe pain and his requirement for morphine had escalated to a dose, which had caused a state of high sedation, which was unacceptable to the patient's quality-of-life expectations. The patient had hence been started on modafinil to counteract the quasi-narcoleptic state induced by morphine. The serendipitous improvement in his neurotoxicity soon after modafinil was started has prompted us to ponder over modafinil's beneficial effects in managing vincristine-induced neurotoxicity.

The case of this patient has been interesting for two reasons. First because uniocular palsy is a very rare manifestation of vincristine-induced neurotoxicity. Second, due to the rather abrupt improvement in his generalised neurotoxicity after starting modafinil.

CASE PRESENTATION

We here describe a 28-year-old gentleman who had received vincristine as a part of his treatment for CD20-negative non-Hodgkin's lymphoma (NHL). There were no previous clinical symptoms of neuropathy and there was no positive history for inherited neuropathies. He had no history of intake of any other drugs known to be neurotoxic. He had received vincristine as part of the cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) regimen for three cycles, which included vincristine being given once every 21 days. His tolerance to the first cycle was good with him not manifesting any

neurological symptoms or signs. However, 15 days after the second cycle, there was an onset of toxicity, which have been graded here using the National Cancer Institute Common Toxicity Criteria version 3.² He manifested grade 2 bilateral motor weakness in his lower limbs. It was also accompanied by mild, tolerable grade 2 paraesthesias, which were not painful.

Four days after the third cycle of CHOP (67th day after initiation of the first cycle), the patient developed severe ptosis of his left eye. Our initial suspicions were of an intracranial neoplastic phenomenon. However, an MRI scan revealed no evidence of intracranial or intraorbital spread. On passive elevation of the eyelid, patient reported undisturbed vision. However, there was a definite inequality in the sizes and reactivity of the pupils. The pupil of the left eye was dilated and sluggishly reactive to light. A cerebrospinal fluid examination was normal too. The patient's sensorium was unaffected.

Concurrently, the patient's peripheral neuropathy also worsened, with him manifesting grade 3 motor neurotoxicity at the knee and ankle joints. However, there was no difficulty in respiration or deglutition. The sensory neuropathy, also worsened to grade 3 painful dysaesthesias in both the upper and lower limbs, for which the patient had not responded to gabapentin.

Then, since the patient complained of excessive somnolence due to morphine, which he had been given for palliation of his pain, he was started on oral modafinil, 200 mg once a day, in the morning.

OUTCOME AND FOLLOW-UP

After 72 h of starting modafinil, there was a remarkable improvement in the motor, sensory and oculomotor neuropathies. Although slight weakness persisted, the improvement was enough to make the patient ambulatory again. The painful dysaesthesias gave way to mild paraesthesias. Thus, his grade 3 motor and sensory neuropathies were downstaged to grade 1. His ptosis improved to grade 1 too.

The patient was continued on chemotherapy with the dose of vincristine reduced from 2 to 1 mg in the subsequent

Figure 1 Unilateral ptosis and unilateral ophthalmoplegia as a rare manifestation of vincristine neurotoxicity.

(fourth and fifth) cycles. The resumption of chemotherapy with reduced dose of vincristine and concurrent modafinil was not associated with aggravation of ptosis or any other neurological toxicities.

However, after the sixth cycle, the patient's disease kept worsening and bone marrow infiltration had occurred. The patient succumbed to septicaemia.

DISCUSSION

Unilateral ocular neurotoxicity is a very rare presentation of vincristine toxicity. A thorough literature search revealed only two previously published cases of patients with vincristine-induced unilateral ocular palsy. In the first of the two previously reported cases, a 28-year-old patient with NHL had presented with an acute onset of diplopia 3 weeks after the completion of combination chemotherapy with vincristine. He had left esotropia with marked decrease in abduction.³ The second report described a 4-year-old girl suffering with B cell acute lymphoblastic leukaemia who developed vincristine-induced unilateral ocular palsy, which was managed with conservative treatment and periodic examinations.⁴

We will now go on to discuss as to how vincristine causes neurotoxicity and about the preventive and remedial measures for vincristine neurotoxicity elucidated in the literature until now. We will then describe as to how modafinil serendipitously helped in this patient and we will justify why, and for what reason, we had chosen to use modafinil in this patient at all.

Vincristine is a unique drug in that its dose is usually capped off at 2 mg irrespective of body weight or surface area. Its predominant dose-limiting toxicity is neurotoxicity. Vincristine is classified as an antimitotic-antimicrotubule agent. We recall that microtubules are those components of the mitotic spindle apparatus that separate the chromosome pairs during mitosis. Microtubules also play other significant roles including, but not limited to, the maintenance of cell shape, scaffolding function, intracellular transport and most notably, intraneuronal transport.^{5 6}

Vincristine induces its cytotoxicity (and neurotoxicity) by interacting with tubulin. Although this agent

classified as an antimitotic, this mechanism may not be its sole mechanism of cytotoxicity in vivo. It can be said so because of the fact that it disrupts interphase microtubules involved in chemotaxis, migratory intracellular transport, movement of organelles, secretory processes, membrane trafficking, transmission of growth factors from cell surface receptor to the nucleus and structural integrity of platelets and other cells, which are rich in tubulin and depend on microtubules for their shape and structure. The neurological effects of vincristine are axonal degeneration and decreased axonal transport as a result of the interference with axonal microtubule function.⁷⁻⁹ Vincristine is administered intravenously as a bolus or a very brief infusion. Its pharmacokinetics is marked by large volumes of distribution, extensive tissue binding and large interpatient variability. Although peak plasma concentrations persist only for a few minutes, the terminal half life is protracted, varying from 23 to 85 h. This is because vincristine, in contrast to the other vinka alkaloids, has a relatively higher tissue binding and lower clearance rate.^{1 5 7}

The neurotoxicity induced by vincristine is classically described to be a peripheral, symmetric, mixed, sensorimotor and autonomic polyneuropathy.^{10 11} As of this date, the only proven remedies for vincristine neurotoxicity are discontinuation, dose reduction and frequency reduction.^{10 12 13} Vincristine does not cause central nervous system toxicity as it does not significantly cross the blood-brain barrier.⁵

The rare adverse reaction of a unilateral ptosis in our patient scored 7 points on the Naranjo algorithm,¹⁴ suggesting a 'probable association' between vincristine administration and the unilateral ptosis. However, we propose that the association was stronger than as suggested by the Naranjo algorithm, owing to the fact that the algorithm contained parameters, which were not applicable to this scenario, for example, the algorithm having assigned weightage to plasma levels of the causative agent. Vincristine toxicity manifests days to weeks after its clearance from plasma and hence, measuring plasma levels of vincristine would not be fruitful. Well described vincristine-induced toxicities such as peripheral neuropathy and

paralytic ileus are dependent more on cumulative dose to the target tissues where extensive binding occurs rather than on acute exposure to a specific plasma concentration.^{1–11} This reason also precludes the possibility of using a dechallenge–rechallenge test to confirm the association.

Pyridoxine and vitamin B12 have been tried as antidotes. But neither has been shown to be consistently beneficial. Ethosuccinimide can be used against painful peripheral neuropathy though it has no effect on the motor deficits. Glutamic acid, ORG-2766 (an adrenocorticotrophic hormone analogue) and noscipine have also been stated to protect against vincristine-induced neuropathy. Folinic acid has also been used successfully in a small number of vincristine overdosages in humans.^{13–15–16}

In our report, we propose that modafinil that was used for another indication in this patient could have acted as an antidote for vincristine neurotoxicity.

Since the exact pharmacological actions of modafinil are still not clearly delineated, at this moment, it would be safe not to speculate as to how modafinil could have helped in hastening the recovery from neurotoxicity. But at the least, we would like to justify the use of modafinil in this patient.

In view of his pain, this patient was on morphine. His dose requirement for morphine was of such a quantity that he would be in a constantly sedated ‘quasi-narcoleptic’ state. Modafinil is a drug classified as an ‘eugemonic drug’. Eugemonics are wakefulness promoting agents that appear to function primarily by increasing catecholaminergic (adrenergic and dopaminergic) and histaminergic activities in the brain. Unlike many other stimulants, eugemonics are less addictive and are not known to induce dependence.¹⁷ Modafinil is a reasonable alternative to caffeine and amphetamines, in that it is a ‘wakefulness promoter’, rather than an ‘anti-sleep drug’.^{17–19} This fact helps us oblige the terminally ill patients on opioids who request for ‘a remedy that would let them be awake when alive’.

As of this date, modafinil has been approved by the US FDA for the treatment of narcolepsy, shift work sleep disorder and excessive daytime sleepiness associated with obstructive sleep apnoea.²⁰

Also, it has been used off-label, with good effect in the treatment of idiopathic hypersomnia, chronic fatigue syndrome, Parkinson’s disease, multiple sclerosis, myotonic dystrophy, opioid-induced sleepiness, cocaine addiction, drowsiness of primary biliary cirrhosis, seasonal affective disorder, postchemotherapy cognitive impairment, cerebral palsy, fibromyalgia and also as an adjuvant antidepressant.^{21–25} Modafinil is reported to also possess neuroregenerative effects. It was also stated to have the ability to reverse MPTP-induced motor disability in marmosets.²⁶

A retrospective review of paediatric patients indicated that modafinil may help in improving tone and ambulation in spastic diplegic cerebral palsy.²⁷ This would further support our claim that modafinil may, through an unknown mechanism, help in improving neuromuscular function in addition to its known eugemonic effects.

The discovery of agents in the future that would help alleviate the toxicities of vincristine would allow the use of this highly effective drug to its full potential. Further data regarding the exact mechanisms of actions of modafinil may allow it to be possibly used for indications of neuroprotection.

Learning points

- ▶ Unilateral ocular involvement in the form of ptosis or palsy in a patient with leukaemia/lymphoma can be a rare manifestation of vincristine-induced neurotoxicity.
- ▶ Vincristine neurotoxicity cannot be quantified by measuring serum levels of the drug as the toxicity is dependent on cumulative neural tissue binding rather than due to high blood concentrations.
- ▶ Many agents have been reported in small studies and reports to be helpful in preventing vincristine-induced neurotoxicity, with even fewer agents been reported to be helpful in established toxicity.
- ▶ Pyridoxine, glutamic acid and perhaps modafinil may be of utility in established vincristine neurotoxicity.
- ▶ Modafinil is a reasonable candidate for trials in established vincristine neurotoxicity in view of its additional benefits such as enhancing quality of life, improving mood, alleviating fatigue and preventing loss of cognition.

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Competing interests None.

Patient consent Obtained.

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