Vincristine-induced Blindness: A Case Report and Review of Literature

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Abstract. *Background: Neurotoxicity is a dose-limiting side-effect of vincristine therapy. Blindness is a rare central neurotoxicity of vincristine with few case reports. Case report: In the present article, we report a rare case of vincristine-induced blindness in a patient with diffuse large B cell lymphoma. Literature search identified eleven published cases of vincristine-induced blindness. We reviewed patient characteristics, chemotherapy used and type of blindness. Conclusion: Vincristine-induced blindness is rare and unpredictable. Prompt recognition and discontinuation of vincristine may lead to recovery of vision.*

Vincristine is a natural alkaloid which acts by binding with tubulin dimers, thus inhibiting assembly of microtubules in the mitotic spindle at the metaphase stage of cell division (1). Neurotoxicity is a common and dose-limiting adverse effect of vincristine, usually occurring as peripheral neuropathy (2, 3). Blindness is a rare central neurotoxicity of vincristine therapy, with eleven reported cases (2, 4-11). We report on a case of vincristine-induced blindness in a patient with lymphoma.

Case Report

A 77-year-old male with stage III diffuse large B-cell lymphoma was started on every three-weekly therapy of rituximab at 375 mg/m^2 d1, cyclophosphamide at 750 mg/m^2 d1, doxorubicin at 50 mg/m^2 d1, vincristine at 1.4 mg/m^2 d1 and oral prednisone 100 mg d1-5 (R-CHOP). His past medical history was significant for hypertension. He also had a history of chronic diplopia and had previously undergone cataract surgery. After the first cycle of chemotherapy, the patient complained of transient ametropia of the left eye. Ocular examination was unremarkable, with intact extraocular movements; pupils were equal, round, and reactive to light and accommodation. There were no significant neurological findings. Magnetic resonance imaging showed no evidence of lymphoma, but confirmed age-related ischemia. Magnetic resonance angiography showed normal blood flow in the ophthalmic arteries bilaterally. Cerebrospinal fluid examination showed glucose of 58 mg/dl, protein of 38 mg/dl, 10 nucleated cells/mm^3, with 85% lymphocytes, 4% neutrophils and 11% monocytes. No specimen was available for further flow cytometric testing.

A positron-emission tomographic scan after the third cycle of treatment showed no evidence of residual metabolically-active disease. Just prior to the fourth cycle of chemotherapy, the patient experienced bilateral blindness. A second vision referral consult diagnosed ischemic optic neuropathy. Although vincristine was eliminated from the fourth and fifth cycles of treatment, the patient's vision did not return.

Discussion

Chemotherapeutic agents, including fluorouracil, methotrexate, mitotane, tamoxifen, busulfan, carmustine, vinblastine and vincristine, may be associated with visual changes, some potentially serious (12). Vincristine-induced ocular toxicity may be manifested as cranial nerve palsy, optic neuropathy/atrophy, or cortical blindness (2, 4, 6-11, 13). Depolarization of neurotubules by vincristine results in neurofibrillary degeneration and impairment of axonal transport (14). Blindness may occur as the result of optic nerve ischemia, primary toxic axonal injury to the retinal nerve fiber layer, or disruption of microtubule polymerization (2, 5, 15). The latter was also found to be associated with impairment of axoplasmic flow and loss of neurosynaptic activity in visual cells, resulting in night blindness (5).

Vincristine has a long half-life (85±69 h) and large volume of distribution (215 l/1.73 m^2), leading to prolonged accumulation in vascular tissue and potential endothelial damage (16). As a result, blood flow to the retina, ganglion cells, axons, and surrounding glial tissue is compromised. Influx of calcium ions *via* sodium-mediated calcium transporters activates proteolytic enzymes, resulting in

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Table I. *Reports of vincristine-induced blindness in literature.*

Author (ref)	Age (years)	Gender	Disease	Prior ocular condition(s)	Chemotherapy regimen used	No. of courses of vincristine	Cumulative dose	Cause/pattern of blindness	Type of blindness
Munier *et al.* (2)	25	F	Kaposi sarcoma	N/A	Vincristine, doxorubicin, bleomycin	11	22 mg	Optic atrophy	Permanent
Byrd *et al.* (4) #1	7	M	Burkitt's lymphoma	N/A	Vincristine,	1	2 mg	Cortical	Transient
#2	3 Years, 11 months	M	Rhabdomyo-sarcoma	N/A	cyclophosphamide, prednisone Vincristine, actinomycin D	3	N/A	Cortical	Transient
#3	11	F	Non-Hodgkin lymphoma	N/A	Vincristine, methotrexate, L-asparaginase, prednisone, cytosine arabinoside, doxorubicin	3	6 mg	Cortical	Transient
Ripps *et al.* (5)	30	M	Malignant melanoma	None	Vincristine, dacarbazine, CCNU, bleomycin	2	8 mg	Night blindness	N/A
Schouten *et al.* (6)	8	M	B-Cell non-Hodgkin lymphoma	None Transient	Vincristine, cyclophosphamide, doxorubicin, prednisone	1	4 mg	Cortical	
Merimsky *et al.* (7)	67	F	Leiomyo-sarcoma	N/A	Vincristine, cyclophosphamide, adriamycin, dacarbazine	1	4 mg	Cortical	Permanent
Awidi (8)	18	M	Diffuse lymphocytic lymphoma	N/A	Vincristine, cyclophosphamide, prednisone	8	16 mg	Optic atrophy	Permanent
Teichmann and Dabbagh (9)	11	F	Astrocytoma	N/A	Vincristine, CCNU, procarbazine	1	2 mg	Optic atrophy	Permanent
Shurin *et al.* (10)	15	F	Medullo-blastoma	N/A	Vincristine, CCNU, prednisone	2	34 mg	Optic atrophy	Partially reversible
Weisfeld-adams *et al.* (11)	6	M	Neuro-ectodermal tumor	N/A	Vincristine, etoposide, cisplatin, cyclophosphamide	6	12 mg	Optic atrophy	Partially reversible

CCNU: 1-(2-Chloroethyl)-3-cyclohexyl-1-nitroso-urea; F: female; M: male; N/A: not available.

axonal damage (17). Ischemia involving the optic nerve may lead to blindness (15).

Optic neuropathy is more likely to occur in patients with cardiovascular risk factors secondary to disruptions in perfusion and autoregulation of blood flow in the vessels supplying the optic nerve (18, 19, 20). Hypertension was the only significant cardiovascular risk factor present in this patient. A medication review failed to reveal any other explanation for ocular toxicities of this nature. The most likely mechanism of blindness in this case was vincristine-induced ischemic optic neuropathy.

Literature review revealed eleven published cases of vincristine-induced blindness, as mentioned in Table I (2, 4-11). These findings demonstrate that vincristine-induced blindness may occur irrespective of age, underlying disease or cumulative dose. Patients who had partial or complete recovery of vision received no additional vincristine after recognition of this complication (4, 6, 10, 11). After discontinuation of vincristine, IV steroids were employed by Weisfeld-Adams JD, et al (11) with slight improvement in vision which remained stable at 1 year follow up.

Conclusion

Ocular toxicity including transient or permanent blindness may occur during treatment with vincristine. Discontinuation of vincristine may lead to recovery of the vision.

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