

Vinca alkaloids induced peripheral neuropathy- case series and review of literature

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Abstract

Vinca alkaloids include vincristine, vinblastine and vinorelbine. Peripheral neuropathy (PN) is one of the commonest side effects of these agents. Patients with decreased level of serum folate and vitamin B 12 are more prone to develop peripheral neuropathy. Underlying hepatic impairment and concurrent drugs which decrease Vinca alkaloids hepatic metabolism also increase the susceptibility to neuropathy. Peripheral neuropathy can be troublesome for significant number of patients. There is no specific therapy for this complication however; symptoms improve with the use of pyridoxine, pregabalin and NSAIDs in some cases. Aim of this case study was to review the characteristics and outcomes of patients who suffered from peripheral neuropathy due to vincristine or vinblastine.

Keywords: vinca alkaloids, peripheral neuropathy, cycles of chemotherapy, serum folate level, dose reduction.

1. Introduction

Vinca alkaloids are group of cytotoxic alkaloids extracted from the Madagascar periwinkle (*Catharanthus roseus* G. Don or *Vinca rosea* L) and used as antineoplastic agent. The group includes vincristine vinblastine and vinorelbine they are cell cycle specific for the M phase of cell division and disrupt the microtubules that form the spindle apparatus. Peripheral neuropathy is a common complication that is associated with the use of vinca alkaloids. The symptoms appear few days of vinca alkaloids administration. Approximately one half of patients develop a sensorimotor neuropathy at normal doses of 1.4 mg/m² per week with vincristine. Neuropathy with vinorelbine is usually mild and has been reported in 14% to 48% of patients receiving a total dose of 30 mg/m². Degree of peripheral neuropathy is greatest with vincristine followed by vinblastine and vinorelbine [1].

Vincristine produces a predictable mixed motor and sensory neuropathy, as well as an autonomic neuropathy. Vincristine-induced neuropathy has been reported to be largely reversible; vincristine may produce a sensorimotor neuropathy and motor dysfunction such as foot drop – while vinblastine causes sensory neuropathy that is also reversible.[2] Vinorelbine causes both sensory and motor neuropathy. Vinca alkaloids are metabolized by hepatic enzymes CYP 3A4. Decrease serum level of folic acid and vitamin B 12, pre-existing neuropathy also increases the risk of vinca alkaloids induced peripheral neuropathy Comorbidities which increase the risk of neuropathy are presence of diabetes, smoking history, and decreased creatinine clearance. Concomitant use of taxanes chemotherapy and drugs such as CYP3A4 inhibitors (Ketoconazole, clarithromycin, ritonavir) increases the risk of vinca alkaloids induced neuropathy. The incidence and severity of neuropathy, depends on the agent used, absolute and cumulative drug dose, administration schedule, and presence of co morbidities. There is no specific treatment for vinca alkaloid induced peripheral neuropathy. The use of pyridoxine is found to be effective for vincristine induced neuropathy [3].

Capsaicin is a topical cream derived from the chilli pepper that may have benefit in PN [4,5]. The mechanism of capsaicin is through depletion of substance P in the distal nerve endings, and therefore may be efficacious for a variety of different types of neuropathy. Paraesthesia and pain are troublesome the patient should be treated with carbamazepine, imipramine or lignocaine [6]. The purpose of this study was to determine the characteristics and the under lying risk factors associated with the development of peripheral neuropathy in our patients.

2. Cases

2.1 Case 1

A 27 years old female patient with the diagnosis of diffuse large B cell lymphoma (DLBCL) stage II B, developed peripheral neuropathy after receiving 3 doses of vincristine 1.4mg/m² as part of CHOP (cyclophosphamide 750mg/m², doxorubicin 50mg/m², of vincristine 1.4mg/m²-all on day 1 and prednisolone 100 mg for 5 days) regimen. She developed

numbness/weakness in legs from feet to mid-calf few days after receiving third dose of vincristine. No complaint was made during previous cycles. Grade 3/4 peripheral neuropathy was declared clinically. Vitamin B12 and folate levels were normal. Renal and liver function and blood glucose were also within normal range. Vincristine was omitted from the chemo regimen. She was started on pyridoxine 50 mg three times per day for one month. PN resolved over time. Disease was refractory to multiple cycles of different regimens including CHOP, DHAP and ICE. Patient died of disease progression.

2.2 Case 2

A 28 years old male, known case of Hodgkin's lymphoma stage IV developed numbness of feet with difficulty in walking. Patient developed symptoms of tingling/numbness and gradual weakness, after receiving three cycles of cyclophosphamide $500\text{mg}/\text{m}^2$, vincristine $1.5\text{mg}/\text{m}^2$, prednisolone $40\text{mg}/\text{m}^2$ and procarbazine $100\text{mg}/\text{m}^2$ based COPP regimen. Examination and nerve conduction studies revealed glove and stocking pattern grade 3 peripheral neuropathy. Baseline renal and hepatic tests were normal. Folate level was on lower side hence folic acid 5 mg once daily was started. Patient was also given pyridoxine 50 mg three times per day. Symptoms resolved overtime. Patient did not respond to first line therapy. After repeat biopsy and confirmation of same disease, second line therapy was started. However, during treatment, patient had neutropenic sepsis and died of multi-organ failures.

2.3 Case 3

46 years old male with DLBCL stage IV, developed numbness of hand and feet post two cycles of CHOP regimen. No dose reduction was considered necessary. His baseline renal and hepatic functions were normal. Post cycle 2, his serum folate and vitamin B12 level were also repeated which were normal. After four cycles of chemotherapy, patient had an excellent response to therapy, but developed severe neuropathy (grade 3). He was started on pyridoxine. During the course of treatment, he was advised pregabalin, tramadol, celecoxib and morphine for pain. Neurological examination revealed power 1/5 in left upper limb with right 6th nerve palsy. His pain worsened over the period of time, involving shoulder and upper limbs. With worsening neuropathy, further investigations revealed CNS involvement. Chemotherapy regimen was changed accordingly however, patient died of disease progression in CNS.

2.4 Case 4

48 years old male a known case of DLBCL stage IV. Following first cycle of CHOP had mild numbness of hands. Baseline biochemical tests were normal. Close observation advised however, with further cycles, numbness got worse.

He was labeled as grade 2 PN and vincristine dose reduced to 50%. Pyridoxine was started with no symptomatic improvement. Symptoms of PN worsened even with omission of vincristine from the regimen. Patient developed multiple cranial nerve palsies and imaging consistent with CNS disease. He was started on multivitamin B complex, pregabalin, celecoxib and tramadol for neuropathic pain without any symptomatic improvement. Patient developed lower limb weakness, slurring of speech and right eye drooping. His chemotherapy was changed accordingly but unfortunately patient died of disease progression.

2.5 Case 5

43 years old male with Hodgkin's Lymphoma stage IV, was started on doxorubicin $25\text{mg}/\text{m}^2$, Bleomycin $10\text{ IU}/\text{m}^2$, Vinblastine $6\text{mg}/\text{m}^2$, Dacarbazine $375\text{mg}/\text{m}^2$ (ABVD) chemotherapy regimen. Two weeks after receiving first dose of chemotherapy he developed lower limbs weakness and numbness. Baseline renal, hepatic functions, B12 and folate levels were normal. Nerve conduction studies revealed peripheral neuropathy. Vinblastine was removed from the chemo regimen. He was started on pyridoxine 50 mg three times and pregabalin 75 mg once daily. These two drugs were continued for several weeks and symptoms of PN improved. Patient continued chemotherapy without vinblastine leading to complete remission however died of bleomycin toxicity.

2.6 Case 6

A 43 years old male diagnosed case of DLBCL stage 1, developed numbness of hand and feet after receiving second cycle of CHOP chemo regimen. He was diagnosed as vincristine induced grade 2 PN. His baseline laboratory tests including B12 and folate were normal. Vincristine was reduced to 50% of normal dose. He was started on pyridoxine with symptomatic improvement in few weeks. He completed his planned four cycles of CHOP regimen and currently in remission.

2.7 Case 7

A 24 years old male known case of DLBCL stage II developed numbness of feet, after receiving first cycle of CHOP chemotherapy regimen. He developed pain in leg and difficulty in walking. Numbness of feet was diagnosed as vincristine induced PN. His baseline renal and hepatic functions were normal. Serum folate level was a bit low for which he was started on folic acid. Serum vitamin B 12 level was within normal limit. He was given pyridoxine 50 mg two times a day. Physiotherapy was also started and symptoms improved. He received 5 cycles of CHOP regimen without any worsening of neuropathy. Unfortunately, post 5th cycle patient had disease progression.

3. Discussion

PN is a well-known side effect of vinca alkaloids. Different risk factors have been proposed to predispose patients to develop PN. Vinca alkaloids are important agents in the treatment of lymphoma. At times, peripheral neuropathy could be very disabling leading to dose reduction or cessation of drug which in turn can affect disease outcome. There is no specific treatment to treat PN however, different medications including multivitamins and specific drugs such as amitriptyline, carbamazepine etc. been tried for symptomatic control. Carbamazepine is a sodium channel blocker and was studied as a neuro-protective agent in patients receiving oxaliplatin further studies are required to confirm this. Time of onset of the symptoms and mechanism of nerve toxicity differs depending upon the chemotherapy agent used. Vinca alkaloids related neurotoxicity is usually dose dependent. Approximately one half of patients develop a sensorimotor neuropathy at normal doses of 1.4 mg/m² per week [7]. For vinorelbine, neuropathy, usually mild, has been reported in 14% to 48% of patients receiving a total dose of 30 mg/m² [8]. Vincristine is most toxic followed by other agents of this group such as vinblastine and vinorelbine. Usual presentation is with sensory symptoms; however, distal weakness like foot drop and autonomic involvement has also been seen. Axonal regeneration may occur by a month after discontinuing the drug [9]. Vincristine related PN is usually reversible however, in some patients mild symptoms persist for several weeks.

In our study, most common symptoms were numbness and tingling of hands or feet. Weakness of arms or legs was also observed in some patients. Most patients developed these symptoms after 3-4 cycles of Vinca alkaloids, showing a dose dependent pattern. Other important point was that almost all patients had advanced stage disease. Two patients later diagnosed to have CNS disease that may be contributing to symptoms of patients as well. So it is important to rule out CNS disease in non-Hodgkin lymphoma patients, in particular if PN symptoms are getting worse even after stopping the culprit agent. PN was observed few days after administration of drugs. Patients showed numbness of hands and feet. Only one out of seven patients had low serum folate acid while rest of parameters. Baseline renal hepatic functions were normal in the listed patients. This is slightly contrary to data available which showed vinca alkaloids induced peripheral neuropathy associated with low serum folic acid level or deranged hepatic functions [10]. More than half of the patients developed peripheral neuropathy after receiving at least 3 doses of vinca alkaloids. This seems a relation with the cumulative dose rather after a single dose incident. Moreover, it became very evident from the study that patients suffering PN had very different risk factors from those described in literature. As most of the literature and research work is done in western countries the result from this study strongly emphasizes the need of local population data and research work so that we may be able to find a comprehensive data to modify drug therapy accordingly.

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