CASE REPORT

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Vinorelbine-induced Acute Reversible Peripheral Neuropathy in a Patient with Ovarian Carcinoma Pretreated with Carboplatin and Paclitaxel

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Vinorelbine is a semisynthetic derivative of vinblastine commonly used for the treatment of advanced breast cancer and non-small cell lung cancer. It has also been tested in other malignancies including ovarian and prostatic carcinoma as well as lymphoma (1). Its antitumoral activity is dependent on the high affinity for mitotic tubulin, which results in the inhibition of both microtubule formation and metaphase cell division. Vinorelbine differs from other vinca alkaloids with regard to its toxicity profile: it seems to be less neurotoxic because of its lower affinity for axonal microtubules. Mild to moderate peripheral neuropathy, principally characterized by sensory effects such as loss of deep tendon reflexes, paresthesia and hypoesthesia, occurs in 6% to 31% of patients; other frequently observed neurotoxic effects include constipation observed in about 30% of subjects, whereas severe toxicity occurs in 2–3% (1). Vinorelbine-associated neuropathy has also been shown to increase with cumulative doses and in patients with pre-existing peripheral neurological impairment; for example, in the case of diabetes mellitus, elevated alcohol consumption and inherited neuropathy. Moreover, concomitant or previous treatment with other potentially neurotoxic drugs such as cisplatin and paclitaxel is associated with a moderate increase in the incidence of acute, severe neurotoxicity.

In this report, we describe a case of vinorelbine-related severe neuropathy following first-line carboplatin and second-line paclitaxel chemotherapy. Moreover, we provide a general review of chemotherapy-induced neurotoxicity, focusing on cisplatin compounds, taxanes and vinca alkaloids.

Case report. An 82-year-old woman without any relevant past medical history was diagnosed with inoperable serous-papillary ovarian carcinoma in January 2002. She received four cycles of carboplatin (AUC 4) up to April 2002. Restaging evaluation with abdominal CT scan revealed disease stabilization. In May 2002, a bilateral salpingo-oophorectomy, total abdominal hysterectomy and omentectomy were performed. The pathological examination revealed a stage III bilateral poorly differentiated ovarian carcinoma. Thereafter, four further courses of chemotherapy with carboplatin were given with a decrease in the CA 125 level from 165 IU/ml to 65 IU/ml. In October 2002, treatment with weekly paclitaxel at a dosage of 80 mg/m^2 was started because of an increase in the CA 125 level up to 125 IU/ml, even though an abdominal gynecological examination and abdominal CT scan were both negative. After the 15th administration of paclitaxel, treatment was discontinued because of progressive elevation of the CA 125 level and evidence of disease progression on CT scan. The patient did not complain of any symptoms of neuropathy at the time of paclitaxel discontinuation. Four weeks later, a third-line course of chemotherapy with vinorelbine was started. After the second infusion of vinorelbine, the patient developed a sudden, grade 3 sensory-motor neuropathy characterized by hypoestesia and mild paresthesia of the lower extremities associated with relevant neuromuscular impairment. The diagnostic work-up included a neurological examination, electromyography, a dorsolumbar spinal cord MRI and an abdominal CT scan. The clinical, electrophysiological and radiological findings strongly suggested an iatrogenic pathogenesis of the neuropathological manifestations. In fact, the MRI did not show any abnormal signal intensity and abnormal mass effect, whereas the neurological and electromyographic studies revealed a bilateral loss of the deep Achilles tendon reflexes, weakness of the lower limbs and a moderate grade paresis of the distal muscles. Vinorelbine administration was promptly stopped; treatment with vitamin B6 (900 mg/day) and gabapentin (900 mg/day) associated with physiotherapy was started. Thereafter, the dose of gabapentin was increased up to 2,400 mg/day. Gradual and progressive improvement in the signs and symptoms was noticed within a few weeks after discontinuation of vinorelbine. Up to four months from the toxic episode the neurological functions have almost completely recovered. Physiokinesis therapy is still ongoing while vitamin therapy has been stopped. Gabapentin is presently administered at the dosage of 300 mg twice daily.

Discussion. Chemotherapy-induced neurotoxicity is a major clinical problem because it represents a dose-limiting side effect of a significant number of antineoplastic drugs and may lead to severe, disabling conditions, thus impairing quality of life (2–6). Little is known about the mechanisms responsible for the development of neuropathy. For most neurotoxic agents, high-dose chemotherapy, combination chemotherapy, concomitant cranial

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radiotherapy as well as intra-arterial or intrathecal injection are more likely to produce neurological complications than standard oral or intravenous therapy. Furthermore, advanced age and pre-existing neurological damage may predispose the patient to chemotherapy-induced neuropathy. Both the time of onset and duration of neurotoxic side effects during antineoplastic treatment may vary with regard to different drugs. In fact, depending on the drug used, these effects can become evident during treatment as well as after treatment, even long after chemotherapy has ended.

Cisplatin induces a predominantly sensory neuropathy that may even start a long time after the end of the course of treatment, and which is dose-dependent and usually reversible, although recovery is often slow (6–8 months). Generally, it becomes evident after exposure to cumulative doses as low as 200 mg/m^2; doses above 400 mg/m^2 always lead to neurological damage (7). Carboplatin neurotoxicity is less common, although its prevalence increases with increasing doses. Oxaliplatin induces rapid onset of sensory symptoms immediately after its infusion that last a few days and are worsened by cold. The pathogenesis of cisplatin-induced neuropathy lies in its affinity with the peripheral nervous system. The compound can accumulate even over a long period in dorsal root ganglion cells and sensory nerves, thus interfering with intracellular transport (2, 7, 8). This behavior may explain the frequent development of neurotoxic effects after cessation of cisplatin therapy. The phenomenon of delayed neurotoxicity is called 'coasting' and, to our knowledge, has not been described in association with other antineoplastic agents. Histologically, a loss of axons and atrophy including gliosis of the dorsal column owing to loss of dorsal root ganglion cells can be observed.

Among the taxanes, paclitaxel may lead to peripheral neuropathy principally characterized by sensory symptoms (distal symmetrical paresthesia, hypoesthesia, loss of joint position sense, painful dysesthesia) and, less frequently, by motor symptoms (progressive distal and/or proximal paresis, myalgia, rarely myopathy); these symptoms generally appear after a cumulative dose below 200 mg/m^2, although a few patients develop neuropathy after a single dose of paclitaxel, especially in the case of concomitant administration of cisplatin, which slowly improves with drug withdrawal (9–11). Several phase II studies have shown that neurotoxicity is less common and severe when paclitaxel is given on a weekly schedule rather than every 3 weeks (12). The disruption of neuronal microtubules and consequent axonal degeneration and demyelination are thought to constitute the pathogenetic mechanism of paclitaxel neurotoxicity (13). Compared with paclitaxel, docetaxel shows less frequent and severe neurosensory and neuromuscular effects.

Vincristine induces a peripheral, symmetric, mixed sensory, motor and autonomic polyneuropathy, at least after a cumulative dose of 5 mg, which improves and regresses after drug withdrawal. Usually the first manifestation is a sensory impairment characterized by distal paresthesia, pain, and loss of deep tendon reflexes followed by motor dysfunction consisting of muscle cramps and severe weakness or even paralysis in the distal muscles. Autonomic neurotoxicity of vincristine is also quite frequent and includes constipation, abdominal cramps, paralytic ileus and urinary retention. Affinity for axonal microtubules leads to axonal degeneration and decreased axonal transport.

Neurotoxic manifestations of vinorelbine are usually less common and less severe than other vinca alkaloids, as shown in a large, randomized trial involving patients with advanced non-small cell lung cancer (NSCLC). In this study, the incidence of neurotoxicity was significantly greater with the combination of cisplatin plus vindesine (17%) as compared with vinorelbine plus cisplatin or vinorelbine alone (7%) (14). Clinical and neurophysiological manifestations of vinorelbine neurotoxicity have been described by several investigators. Pace et al. reported a prospective detailed neurological and electrophysiological evaluation in patients treated with weekly vinorelbine at 25 mg/m^2: the majority of patients developed a sensory–motory distal symmetric axonal neuropathy and the degree of neurotoxicity increased with the cumulative dose of vinorelbine and partially recovered after discontinuation of treatment (15). Mild to moderate peripheral neuropathy occurs in 7% to 31% of patients treated with vinorelbine, whereas severe toxicity has been reported in only a few cases and is particularly associated with concomitant or previous treatment with paclitaxel. In 1994, Dittrich et al. described the occurrence of clinically relevant neurotoxicity caused by vinorelbine in patients with advanced breast cancer who had progressed under previous therapy with paclitaxel. In 2 out of 8 consecutive patients treated with 30 mg/m^2 every 2 weeks, vinorelbine administration had to be discontinued because of grade 3 sensory neuropathy after 2 and 3 courses of therapy, respectively (16). A phase II study was later performed by the same group to evaluate both the efficacy and toxicity of vinorelbine in patients with advanced breast cancer failing first- or second-line chemotherapy with paclitaxel. Vinorelbine was given at 30 mg/m^2 at 2-week intervals for the first four courses and thereafter every 3 weeks (17). In 4 out of 14 patients, therapy had to be discontinued because pre-existing peripheral neurotoxicity increased from grade 1 or 2 to grade 3 after 1 to 3 cycles of chemotherapy. Severe neurotoxicity from the combination of vinorelbine and paclitaxel has also been observed in patients with mild pre-existing neuropathy resulting from previous administration of paclitaxel (18). Moreover, a case of vinorelbine-associated myelopathy has been described in a 58-year-old woman with metastatic lung cancer who first received six courses of paclitaxel and carboplatin and then after a one-year interval, vinorelbine infusions (19). All these observations indicate that the combination of vinorelbine plus paclitaxel is associated with a higher risk of developing severe neurotoxicity. The underlying, synergistic effect in inducing neuropathy is not well known.

Our case is remarkable in that the onset of symptoms was not preceded by any neuropathic manifestations from earlier treatment with paclitaxel and carboplatin. Neuropathic disorders were acute and severe, compromising de-ambulation and interfering with activities of daily living. These manifestations developed unexpectedly and immediately after a low cumulative dose of vinorelbine without any pre-existing symptoms.

These observations suggest the possibility of cumulative neurotoxicity of vinorelbine and paclitaxel. Paclitaxel could have induced latent neuronal damage that became clinically evident only after vinorelbine administration. Considering the potential neurotoxicity of carboplatin, we cannot rule out that pretreatment with this agent might also have played a role in the onset of this unusual neurotoxicity. Furthermore, the rapid and almost complete recovery of the neurological signs and symptoms after treatment discontinuation also strongly supports the iatrogenic pathogenesis, excluding other underlying mechanisms. Gabapentin, which is considered a reasonable first choice for the treatment of sensory neuropathy, might have contributed to the improvement in signs and symptoms.

On the basis of our observation and previous reports, we suggest that a careful, preliminary evaluation of paclitaxel-pretreated patients should be made before starting vinorelbine therapy. Clinicians should recognize the importance of collecting an accurate medical history, to perform a neurological assessments and, where indicated, electrophysiological studies in order to prevent the onset or progression of neurotoxicity. Advanced age as well as a short interval between subsequent lines of chemotherapy may represent additional risk factors for the development of neuropathy. Further reporting of the neurological toxicity profile of

vinorelbine-containing regimens following paclitaxel/cisplatin therapy is important in order to clarify the safety of this sequential treatment.

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