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Acute Pain Syndrome at Tumour Site in Neoplastic Patients Treated With Vinorelbine: Report of Unusual Toxicity

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VINORELBINE (VNR), 5'-nor-anhydrovinblastine, is a new semi-synthetic vinca alkaloid with selective activity for mitotic microtubules, which has been shown to be active *in vitro* against several non-small cell cancer lines [1, 2]. VNR has been reported to yield a 34.7 and 20% overall response rate in patients with squamous cell lung carcinoma and bronchial adenocarcinoma, respectively [3]. Moreover, VNR has been shown to be active in advanced breast carcinoma where it may induce a 30–50% response rate, depending on the extent of pretreatment [4–6], and yield a 22% partial response rate in a series of patients with recurrent squamous cell head and neck carcinoma [7].

At our Institution, a total of 1156 intravenous (i.v.) adminstrations of VNR at the dose of 25 mg/m^2 as an i.v. bolus or 20-min infusion have been given in the last 18 months to 150 patients with advanced and/or metastatic lung (n = 47), head/neck (n = 72), breast (n = 12), vulva (n = 6), ovary (n = 3) and uterine carcinomas (n = 10). Most of these patients had metastatic or recurrent disease after primary surgery and/or radiotherapy. Patients with breast cancer had been pretreated with adjuvant hormonotherapy and/or chemotherapy, while the majority of patients with lung cancer were previously untreated. None of these patients had a medical history positive for neurological or significant rheumatological diseases.

After VNR administration 12/150 patients developed acute, often intense and very distressing pain at the tumour site and/or along the distribution of body territory depending on the nerve compressed by the recurrent tumour. Among these 12 patients, 4 were asymptomatic before VNR administration, and 8 patients had mild to moderate locoregional pain due to compressive neoplastic masses before starting chemotherapy. This acute pain appeared immediately after or within 30 min of vinorelbine administration, and lasted from a few minutes up to 1 h, despite symptomatic treatment.

This pain syndrome was observed in 9 patients with squamous cell head and neck carcinoma recurrent after surgery, 1 patient with head and neck carcinoma recurrent after surgery and radiotherapy, and in 2 patients with recurrent adenocarcinoma of the endometrium who had been previously treated with surgery plus adjuvant radiotherapy.

After VNR administration, patients with recurrent carcinoma of the endometrium had pain at the lower left limb, while those with recurrent head and neck carcinoma had pain in the head, neck or shoulder areas independently of the VNR schedule employed (bolus versus infusion). No patient with lung, ovary, breast or vulvar carcinoma showed such episodes. Patients reporting such acute pain syndrome did not show significant concomitant signs of neurosensory toxicity, such as paraesthesias or neuromotor toxicity, and a neurological examination carried out after the painful episodes failed to reveal any sign of permanent neurosensory or neuromotor toxicity. All patients developed pain immediately after the first dose of VNR. Patients who enjoyed a major objective response with reduction of neoplastic lesions and compressive phenomenon did not present pain after a second administration of VNR, while 4 patients who did not show a dimensional reduction of neoplastic lesions experienced a second pain episode when VNR was recycled. Thereafter, VNR administration to these patients was withdrawn. It may be important to stress that all these patients were treated with vinorelbine in combination with high dose (80–120 mg/m^2) cisplatinum. Thus, possible cooperation of VNR with cisplatinum in the genesis of the pain episodes cannot be ruled out.

This acute pain syndrome was empirically managed with non-steroidal anti-inflammatory drugs, such as ketorolac–trimetamine, and steroids. In most cases, prompt therapy as described above resulted in a rapid and complete control of pain. However, in few cases, pain required repeated and frequent i.v. administrations of analgesic drugs, and in one case, i.v. pentazocine was used.

We were not able to discriminate between an acute neurotoxic effect of vinorelbine and pain due to an increase in compression due to swelling of the neoplasm as a consequence of antiblastic drug administration. However, no signs of classical neurotoxicity of vinca alkaloids[6] were recorded in these cases. A possible relationship with previous radiotherapy is lacking, since 75% of cases occurred in patients who had received only surgery. However, it should be noted that all patients suffering from this pain syndrome had bulky recurrent disease which could have caused nervous compression, even if subclinical. Oncologists should be aware of this unusual side-effect of VNR which, if unexpected, may be distressing for both patients and physicians.

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