Short report

Acute pulmonary toxicity associated with high-dose vinorelbine and mitomycin C

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Introduction
Vinorelbine (VNB), 5-nor-anhydrovinblastine, is a new semisynthetic vinca alkaloid with a broad spectrum of antineoplastic activity both in vitro [1] and in vivo. Promising therapeutic results have recently been reported in different tumour types, including lung, breast, head and neck cancer, and Hodgkin's disease [2]. Data from clinical trials indicate that VNB is safe and well tolerated, with neutropenia being the most common and dose-limiting toxicity [3]. Nonhematologic adverse reactions are mostly mild or moderate, and because of the selective activity for mitotic microtubules [4], drug-associated neurotoxicity occurs less often than with other commonly used, natural vinca alkaloids. Respiratory reactions have only rarely been observed in patients treated with VNB [3]. We report here a case of acute, severe pulmonary toxicity in a patient receiving high-dose VNB and mitomycin C (MMC) for treatment of advanced breast cancer. A toxicity analysis of 87 patients treated with similar VNB dose regimens, that has been performed in view of this case, revealed a total of 16 episodes of this unusual, most likely allergic, adverse reaction.

Case report
A 45-year-old woman suffering from recurrent breast cancer was admitted to our institution in October 1993. After having undergone quadrantectomy and axillary dissection for a (hormone-receptor positive) moderately well differentiated pT2N0 ductal breast cancer in September 92, she received adjuvant breast irradiation and hormonal treatment with tamoxifen/goserelin. In July 93, intrahepatic tumour recurrence was diagnosed. A total of 3 cycles of combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) were administered until progressive disease was noted in September 93. The patient was subsequently entered in a phase II trial and received second-line therapy with VNB 50 mg/m² in 250 ml saline administered intravenously (i.v.) over 30 minutes on days 1 and 21 plus MMC 15 mg/m² given by i.v. bolus injection on day 1. To prevent/counteract myelotoxicity, human granulocyte colony-stimulating factor (G-CSF) was injected subcutaneously at 5 μg/kg/day from days 2 to 7 following each cytotoxic drug administration. Treatment cycles were repeated every 6 weeks. Because of the absence of any adverse reaction during the first course, treatment was continued on an outpatient basis. On day 21 of her 3rd course, approximately 1 hour after the infusion of VNB, the patient experienced acute onset of progressive, severe dyspnea with clinical signs of obstructive lung disease. On admittance to the intensive care unit, a chest X-ray and CT-scan disclosed bilateral interstitial infiltrates, a finding that had not been noted during a routine radiologic examination 3 weeks before. There was no evidence of a pleural effusion, and blood chemistry including a complete blood cell count and differential count were without abnormal findings.

The patient required respirator support for 18 hours. Treatment with bronchodilators and corticoids resulted in a continuous improvement of symptoms. The patient was transferred to a normal ward on the next day with only slight dyspnea not interfering with everyday activities. The radiologic abnormalities had completely resolved approximately 48 hours following the onset of symptoms. After a further observation period of 3 days, the patient was discharged from hospital with complete resolution of respiratory complaints. Despite radiologic evidence of partial tumour regression, treatment with VNB/MMC + G-CSF was discontinued and changed to 3rd-line therapy with fluorouracil, epirubicin and cyclophosphamide (FEC). Shortly after initiation of this therapy, the patient developed lung and bone metastases and died of progressive disease in May 94.

It seems noteworthy that the patient had no prior
history of allergic reactions, pulmonary disease, and (except for a cumulative dose of MMC of 45 mg/m$^2$) there was no evidence of a predisposing condition rendering her particularly susceptible to this adverse reaction.

**Retrospective toxicity analysis of 87 patients**

Analysis of the toxicity data of 55 patients treated with the same high-dose VNB/MMC + G-CSF regimen [5] and of 32 additional patients with advanced breast cancer receiving 4-weekly courses of VNB 40 mg/m$^2$ (days 1 + 14) and l-leucovorin (LLV) 100 mg/m$^2$ plus 5-FU 370 mg/m$^2$ both given on days 1–5 [6], disclosed a total of 16 cases of acute, though generally less severe pulmonary toxicity. Thus, 16/87 (18%) patients (including the case reported above) developed respiratory symptoms while on treatment with high-dose VNB combination regimens. Of these, 14 patients were treated with VNB/MMC + G-CSF and 2 patients with VNB plus LLV/5-FU. Side effects occurred during the 2nd treatment course in 10 patients, and during the 3rd and 4th course in 5 and 1 patient, respectively. Pulmonary toxicity manifested as mild dyspnea (WHO grade 1) in 4 patients, it was rated grade 2 in 6, and in 5 patients symptoms were severe (4 patients treated with VNB/MMC and 1 treated with VNB/5-FU/L-LV), including the reported case with life-threatening toxicity. It seems noteworthy that in 1 patient with grade 3 toxicity, the onset of respiratory symptoms was accompanied by exanthematic skin lesions. In all 5 patients with severe lung toxicity, therapy was discontinued prematurely. In the remaining patients, who had experienced mild or moderate symptoms, the dose of VNB was reduced to 30 mg/m$^2$, and 8 mg of dexamethasone were routinely co-administered during subsequent courses. In these patients symptoms did not recur or were only minimal. There was one patient with a history of asthma bronchiale, however, who despite these measures developed recurrent grade 2 lung toxicity. Apart from interstitial pulmonary infiltrates in the case presented above, no radiologic abnormalities were found on conventional planar chest X-rays ± CT-scans.

**Discussion**

Despite accumulating clinical experience with the use of VNB in the treatment of several different types of malignancy, the occurrence of lung toxicity associated with administration of this agent has only occasionally (<5%) been reported [3]. In fact, two types of respiratory reactions have been described with VNB: an acute reaction with bronchospasm that seems to be allergic and a subacute reaction (as in the present case) characterized by cough and dyspnea occurring within 1 hour after drug administration, sometimes associated with lung infiltrates. Concerning the natural vinca alkaloids vinblastine and vindesine, there is also very limited information about pulmonary adverse reactions [7–9]. Enhanced MMC-related lung toxicity by co-administration of vinca alkaloids has been described by Ozols et al. [8]. Five patients receiving MMC, vinblastine and progesterone developed lung toxicity with radiologically detectable bilateral pulmonary infiltrates. Post mortem findings revealed evidence of pulmonary fibrosis, as has been seen with the administration of MMC alone. In all these cases, MMC was administered along with the vinca alkaloid. In the present series, however, there are a number of features that strongly argue against a simple enhancement of MMC-related lung toxicity by co-administration of VNB. First, the symptoms experienced by our patients were different from typical MMC-associated lung toxicity, which is characterized by a slow and delayed onset of symptoms with a protracted course. All our patients developed a more or less abrupt onset of shortness of breath during or shortly after administration of VNB, usually on a day when the drug was given alone during the 2nd, 3rd or 4th treatment cycle. Second, pulmonary symptoms were also noticed in 2/32 patients who received VNB combined with FU/LLV, in a subsequent phase II trial [6]. Both of these patients were chemotherapeutically-naive, i.e., they had not been previously exposed to agents with potential pulmonary toxicity such as MMC. Third, chest X-rays that were routinely performed in all our patients, disclosed radiologic abnormalities in only 1 case with complete resolution of all visible changes within 48 hours after VNB exposure. The transient and acute nature of respiratory symptoms associated with VNB, recurrent symptoms in a patient with allergic diathesis (i.e., a history of hay fever), and the fact that one patient developed concomitant allergic exanthema suggests a delayed hypersensitivity reaction as the most likely pathogenetic mechanism responsible for the toxicity observed in our patients. Because all adverse events appeared during the 2nd treatment cycle or later, sensitization during previous courses seems likely to have occurred.

Co-administration of MMC, which is known to enhance pulmonary toxicity of natural vinca alkaloids [7–9] and has been reported to be associated with a similar reaction of acute bronchospasm in patients receiving a combination regimen with VNB and cisplatin [10], prophylactic use of G-CSF and/or use of higher single doses of VNB compared to those given in most other trials reported until today, are likely to account for the rather common occurrence of this reaction in our series. Whereas a possible contributing role of G-CSF seem unlikely because of the absence of a time-relationsship between respiratory symptoms and administration of the hematopoetic growth factor, the latter seems to be an important point due to the absence of such complications in a previous trial using conventional (30 mg/m$^2$) doses of VNB and MMC [11]. Whether there were also certain pretreatment features rendering our patients more susceptible to this
adverse reaction is difficult to answer in retrospect, though it seems noteworthy that 2/18 had a history of allergic diathesis (one patient with asthma bronchiale and one with a chromium-nickel-allergy). Other possible explanations include routine administration of corticoids together with serotonin antagonists as antiemetic prophylaxis in some trials of VNB combination therapy, which might have prevented/abrogated hypersensitivity reactions. Furthermore, since VNB is commonly employed in patients with lung cancer, mild or moderate respiratory symptoms might have been attributed to the underlying disease rather than to cytotoxic therapy with VNB.

Further investigation of the allergic potential of VNB along with the identification of possible predisposing risk factors seem warranted. In addition, clinicians should be aware of this possible side effect and should consider routine clinical monitoring of patients for acute respiratory symptoms during high-dose VNB administration, especially if given in combination with MMC.

References


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