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SHORT COMMUNICATION

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Vinorelbine-related acute cardiopulmonary toxicity

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Abstract Three cases of possible acute cardiopulmonary toxicity following the administration of vinorelbine are reported. The symptoms mimicked acute cardiac ischemia. However, neither ECG changes nor elevations of serum enzymes were observed. The outcome is favorable in 90% of patients developing this adverse event. The putative mechanism remains to be elucidated.

Key words Vinorelbine · Vinca alkaloids · Cardiac toxicity · Pulmonary toxicity

Introduction

Vinorelbine (VRL) is a vinca alkaloid derivative that plays an important role in the treatment of several malignancies, such as non-small-cell lung cancer (NSCLC), breast carcinoma and ovarian cancer, and of hematological malignancies. Most of the toxicity associated with VRL administration is hematological and gastrointestinal [4]. Repolarization disorders, precordial pain, acute myocardial ischemia, and acute infarction are only rarely reported, especially in association with the other vinca alkaloids, i.e., vincristine, vinblastine, and vindesine [1, 5, 6, 10]. Recent publications refer to the pulmonary and cardiac toxicity of VRL: acute pulmonary edema occurring immediately after the intravenous administration of VRL [9] and acute ischemic event or myocardial infarction being observed during or soon after VRL infusion [2, 7, 11] in patients with various malignancies. Herein we report on three cases, including one of pulmonary edema in association with the intravenous administration of VRL and two of acute precordial pain compatible with that of acute coronary insufficiency.

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Case reports

Case 1

A 52-year-old woman with a 6-year history of T1cNOMO infiltrating ductal carcinoma of the left breast was treated 6 years ago by lumpectomy and axillary nodal dissection followed by radiation therapy (^{60}Co, 2 tangential fields, 50-Gy midplane dose delivered in 25 fractions over 5 weeks). At the end of a 5-year disease-free period she developed bone metastases, indicating palliation by 3-weekly combination chemotherapy with cyclophosphamide at 500 mg/m^2, Adriamycin at 50 mg/m^2, and 5-fluorouracil (5-Fu) at 500 mg/m^2 (CAF) for six courses until May 1997. A partial response was achieved. Since the left ventricular ejection fraction (LVEF) asymptomatically dropped from 58% to 47%, the CAF combination was replaced on August 1997 by weekly injections of 30 mg/m^2 VRL. The first two injections were uneventful except for the occurrence of afebrile neutropenia (500 cells/mm^3) necessitating a 1-week delay in the administration of the next dose. Several minutes after getting the third intravenous VRL injection she felt mild breathlessness. Tachypnea, rales, and wheezing were found on examination. Rapid improvement was noted on inhalation of salbutamol. The fourth dose was given as scheduled, but this time the patient developed severe dyspnea and wheezing that was unresponsive to inhalation of Ventolin and intravenous administration of 300 mg hydrocortisone, requiring admission. A plain chest film demonstrated pulmonary congestion compatible with pulmonary edema and bilateral pleural effusion. The ECG and echocardiogram were unremarkable. O_2 saturation was 78%, and the creatine phosphokinase (CPK) level was not elevated. The patient responded well to diuretics (furosemide at 120 mg) and oxygen support. Pleural puncture yielded 1300 ml clear sterile fluid without malignant cells. Computerized tomography of the lungs, carried out after her stabilization, did not show any pulmonary involvement by malignancy.

Case 2

A 60-year-old woman who was a heavy smoker with an 8-year history of stage I cancer of the left breast was treated by mastectomy

Table 1 Vinorelbine-induced cardiac toxicity (*sq.c.c* Squamous-cell cancer, *CIS*, *CDDP* cisplatin, *CARBO* carboplatin, *MI* myocardial infarction)

Sex/age (years)	Primary	Stage	Treatment	Toxicity/outcome	Reference
M/67	Lung sq.c.c	T2N3M1	VRL + CIS	Dyspnea, crepitation tachycardia/recovery	[3]
M/59	Lung sq.c.c	T1N3M0	VRL + CDDP	Respiratory distress, hypoxemia/recovery	[3]
F/73	Lung sq.c.c		VRL + CDDP	MI, shock, pulmonary edema/recovery	[2]
M/55	Lung sq.c.c		VRL + CARBO	Precordial pain, MI/recovery	[2]
M/76	Lung broncho-alveolar carcinoma	T1N0M0	VRL	MI, complete A-V block	[4]
M/87	Lung non-small-cell cancer	Locally advanced	VRL	MI/recovery	[5]
M/62	Lung sq.c.c	T2N2M0	VRL	MI, cardiogenic shock/death	[6]

in another center. Following a 7-year disease-free period she developed a pulmonary mass in the left upper lobe associated with supraclavicular lymphadenopathy. The node was aspirated and found to harbor metastatic adenocarcinoma compatible with primary lung cancer. Radiation therapy to the mediastinum (44 Gy) and left upper lobe (68 Gy) was given. The disease progressed in the chest within the next 5 months, and the patient was referred to our center. Revision of the tissue taken from the supraclavicular node revealed metastatic carcinoma of the breast. She was treated by 3-weekly CAF combination chemotherapy for six courses until October 1997. No objective response was observed. The LVEF was 60%. The treatment was replaced by VRL given weekly at 30 mg/m^2 and 5-FU. During the first dose of VRL the patient started to complain of severe chest pain. The infusion was interrupted, and the pain was alleviated by sublingual administration of isosorbide dinitrate. Her ECG and CPK level were within the normal range. The patient was hospitalized for observation, which was uneventful.

Case 3

A 61-year-old woman who was a heavy smoker with no history of coronary heart disease or hypertension presented with metastatic squamous-cell lung cancer. Chemotherapy consisting of cisplatin given at 100 mg/m^2 on day 1 every 3 weeks and of given at VRL 25 mg/m^2 on days 1, 8, and 15 was prescribed in January 1997. The day-8, but not the day-15, dose of VRL was omitted due to asymptomatic thrombocytopenia. Soon after she had started the second cycle with the day-1 dose of VRL and before the infusion of day-1 cisplatin she started to complain of typical pressing precordial pain that lasted for 20 min and resolved after the administration of 5 mg isosorbide dinitrate. There was no ECG changes or elevation or serum enzyme levels. Cisplatin was given with a 2-h delay.

Discussion

Our cases point to the possible association between VRL infusion and the development of cardiopulmonary symptoms clinically mimicking acute cardiac ischemia. The symptoms included chest pain, dyspnea, and restlessness accompanied by rales and wheezing on examination and a radiographic picture of pulmonary congestion, although ECG changes and serum enzyme elevations were not observed. In all cases this syndrome appeared within the first three administrations of VRL.

The possible association of VRL treatment and cardiac toxicity has been suggested in several case reports, which are summarized in Table 1. Of three patients with lung cancer who developed myocardial ischemia [2, 7], two never had acute anginal syndrome or evidence of peripheral vascular disease. In both of the cases reported by Bergeron et al. [2] the close temporal relationship between the administration of VRL and the onset of symptoms provides a strong argument in favor of an adverse effect of this drug. The authors concluded that acute myocardial ischemia might develop in association with VRL administration, even in patients with no prior coronary disease. In two cases reported by Vaylet et al. [9], acute pulmonary edema was evident soon after the intravenous administration of VRL. The two patients were heavy smokers who had non-small-cell lung cancer but showed no cardiac symptoms. The patients recovered within short periods, and no ECG change was noted. It should be emphasized that fatality was observed in one of the reported cases [3].

Other drugs belonging to the vinca alkaloid group, namely, vincristine, vinblastine, and vindesine, have also been reported to be associated with cardiac adverse events such as repolarization disturbances, cardiac insufficiency, coronary atherosclerosis, ischemic event, and infarction [1].

Several predisposing factors could have contributed to the development of VRL associated cardiopulmonary toxicity. One patient was irradiated in the left breast and treated with doxorubicin. Two patients had smoked heavily prior to their diagnosis and treatment. One patient had been irradiated in the mediastinum for a previous disease. These risk factors have also been reported by other authors in association with other vinca alkaloids [1].

The putative mechanism responsible for cardiac adverse events related to the administration of VRL and other vinca alkaloids remains obscure. Several explanations have been suggested in the literature, among which are vasoconstriction mediated by a substance released during the injection of VRL and other vinca alkaloids [7]; a direct enhancing effect of the alkaloids on

the coagulation mechanism, leading to arterial occlusion [6, 10]; transient coronary spasm aggravated by coronary atherosclerosis as also reported in relation to 5-Fu administration [8]; a direct effect on the myocardium leading to cellular anoxia [7]; and disorganization of the cellular microtubuli as well as impairment of cellular metabolism and of the contractility of myofibrils [6].

In conclusion, the VRL associated cardiopulmonary toxicity encountered in our patients was severe but not life-threatening. For safety considerations, administration of VRL was not repeated in these patients. Considering all the cases reported in the literature, the fatality rate of VRL associated cardiac toxicity is 10%.

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