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CLINICAL TRIAL REPORT

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Typhlitis (neutropenic enterocolitis) after a single dose of vinorelbine

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Abstract We report a case of a 50-year-old man with pretreated adenocarcinoma of the lung, who developed fatal neutropenic enterocolitis (typhlitis) after a standard dose of the cytotoxic drug vinorelbine. Blood cultures were negative for all microorganisms tested for. Stool cultures were negative for enteric rods but direct examination of fresh stool revealed the presence of *Giardia lamblia*. Abdominal pain and diarrhoea developed very rapidly while the patient was only moderately neutropenic. Metronidazole was prescribed without clinical benefit: the abdominal pain remained stable. The duration of neutropenia was very short (4 days).The abdominal catastrophe ending in shock occurred after complete recovery of the neutrophil count. Neutropenic colitis has been reported with increasing frequency in solid tumours after the introduction of taxanes. This complication has been observed mainly in phase I studies, near the maximally tolerated doses (MTD). The combined use of vinorelbine has recently been reported to exacerbate the toxic effects of taxane on the colon. The case presented here demonstrates that typhlitis can occur even with vinorelbine alone, used at a standard recommended dose (30 mg/m^2).

Key words Taxanes · Typhlitis · Vinorelbine

Introduction

Vinorelbine, 5′-noranhidrovinblastine, is a semisynthetic vinca alkaloid, widely used in cancer chemotherapy [11]. During phase I studies, a maximally tolerated dose of 45 mg/m^2 has been reported, with neutropenia and constipation being dose limiting [8].

Recently, the combined use of vinorelbine with docetaxel caused colitis-like symptoms in three patients. Two patients died. It has been suggested that vinorelbine might exacerbate the toxic effects of taxanes at the colonic level [6]. Here we report on a patient with pretreated adenocarcinoma of the lung who developed clinical signs of typhlitis and died in shock after being treated with vinorelbine at the recommended dose (30 mg/m^2). At autopsy, there were histological signs of necrotizing colitis. Bilateral adrenal metastases were also present, but we favour typhlitis as the cause of death.

Case report

A 50-year-old man with adenocarcinorna of the lung and bilateral adrenal metastases had been previously treated with six cycles of the combination of cisplatin and gemcitabine.

At a follow-up clinical examination after 3 months, he was found to have a progressive disease. A second line of chemotherapy was discussed with him and he received 30 mg/m^2 vinorelbine. After 5 days, he was admitted to our ward because of mental confusion, anaemia, abdominal pain, and diarrhoea. He was moderately neutropenic (neutrophils 900/m^3) and afebrile. He received two units of packed red cells. On the second day of hospitalization, his neutropenia worsened to 170 neutrophils/m^3 and he became febrile.

Intravenous fluids and electrolytes were given along with broad-spectrum intravenous antibiotics. The clinical course is depicted in Table 1.

Abdominal pain was initially interpreted as vinorelbine neurotoxicity. The plain chest X-rays of the abdomen showed significant dilatation of the colonic loops but no air-fluid. On the third day of hospitalization, direct examination of fresh stool showed *Giardia lamblia*. Metronidazole was prescribed without clinical benefit: the abdominal pain remained constant.

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Table 1 Clinical course of the patient

	Day					
	5th	6th	7th	9th	10th	12th
HTC (%)	21.7	28.5	31.6	31.5	31.2	41.7
WBC (μL)	1800	1110	700	340	2300	12,630
Neutrophils (/m^3)	900	170	120	40	800	8790
Temperature (° C)	37.2	38.5	38.5	38.5	37.7C	36
PA (mmHg)	105/60	120/70	130/70	120/70	120/70	50/70
Abdominal pain	+ + + +	+ + + + +	+ + + + +	+ + + +	+ + +	+ + +
Diarrhoea	+ + + +	+ + + + +	+ + + + +	+ + + +	+ + +	+ + +
Stool cultures		*Giardia*				
Blood cultures	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

Neg., negative

After two days of the initial therapy, the patient was still febrile and teicoplanin was added to his treatment regime. The patient was also given G-CSF (granulocyte colony-stimulating factor) at a dose of 300 μg on the 8th and 10th days after the vinorelbine administration. After a short period of profound neutropenia (four days), the neutrophil count of the patient recovered and he became afebrile. Blood cultures remained negative throughout and, on the sixth day of hospitalization, the patient's abdominal symptoms were improving.

On the seventh day of hospitalization, the patient developed unmistakable signs of acute shock, with his arterial pressure dropping to 80/50 mmHg. Despite intense fluid resuscitation and treatment with vasopressors, the patient died the same evening.

Necroscopy showed significant dilatation of the colonic loops, accompanied by thickening of the walls of mainly the cecum but also extending to the ascending colon. Histological examination showed necrotizing colitis.

The colonic mucosa showed large areas of ischemic necrosis accompanied by inflammatory infiltrate, diffuse crypt dropout, and loss of surface epithelium (Fig. 1).

Stool cultures were negative for Gram negative rods, but direct examination of the stool found *Giardia lamblia*. It is, however unclear whether *Giardia* might have contributed to the severity of the intestinal infection in this patient.

Fig. 1 (Photograph) Histological sample of the colon taken at necroscopy. Ischemic damage is present along with loss of surface epithelium

Discussion

Neutropenic enterocolitis (typhlitis) used to be a rather infrequent finding in patients with solid tumours [4]. However, with the introduction of new drugs, particularly the taxanes in cancer chemotherapy, this complication has been reported with increasing frequency [1, 2, 3, 4, 5, 6, 7, 8, 9]. It has commonly been observed near to MTD in combination studies. Epithelial necrosis in the gastrointestinal tract was found to be associated with the typical polymerized microtubule accumulation and mitotic arrest induced by taxanes [5].

Recently, investigators from MD Anderson [9], reported on three patients who were treated in a phase I study combining docetaxel, vinorelbine, and C-GSF. One patient died from a necrotic bowel and the other from neutropenic fever and colitis. Three other patients, treated with Docetaxel alone and combined with other drugs, developed clinical and radiological signs of colitis but recovered eventually [6].

It has been suggested that these two classes of anticancer compounds may have the propensity to cause necrotizing colitis in common. The role of neutropenia is less clear; in some cases, this complication occurred even in the absence of neutropenia [6]. Our case report documents for the first time the occurrence of clinical and pathological signs suggestive of typhlitis in a patient receiving vinorelbine alone at a standard recommended dose.

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