Typhlitis Associated With Docetaxel Treatment

Typhlitis, previously known as a serious complication of hematologic malignant and nonmalignant conditions (1,2), is now being described with increasing frequency in solid cancers following aggressive chemotherapy (3-5).

Severe neutropenia is the underlying factor in all patients with typhlitis, also called neutropenic enterocolitis. We report a patient with lung cancer who developed typhlitis and fatal sepsis due to Clostridium septicum after a single dose of docetaxel (Taxotere, Rhone-Poulec-Rorer Pharmaceuticals, Inc., Paris, France).

A 46-year-old man was admitted with an 8-hour history of lower abdominal pain, fever, and vomiting. He had been diagnosed with locally advanced squamous cell carcinoma of the lung 8 months earlier and treated with cisplatin and vinblastine. Two months after the last vinblastine dose, he was given docetaxel at a dose of 100 mg/m² (200 mg total) in a 1-hour infusion. The patient had a World Health Organization (WHO) performance status of 1 and had normal liver function tests. He also received methylprednisolone at a dose of 24 mg orally twice a day for 4 days. Five days after docetaxel treatment, he developed a transitory erythematous maculopapular rash, arthralgia, myalgia, and asthenia.

On admission, the patient was prostrated and had a temperature of 37 °C, a pulse rate of 100 beats per minute, a respiration rate of 28 breaths per minute, and a blood pressure of 100/80 mm Hg. Mild signs of abdominal peritonism were also detected. Laboratory tests revealed a white blood cell count of 1500/mm³, an absolute neutrophil count of 200/mm³, a hemoglobin level of 13.7 g/100 mL, and a platelet count of 326 000/mm³. The serum amylase level was 182 U/L (normal level, <119 U/L). An abdominal x ray showed small bowel distension. He was started on intravenous fluids, ceftazidime (2 g every 8 hours), and amikacin (500 mg every 12 hours). In 3 hours, he went into shock and, despite all supportive measures, died 11 hours following admission. Blood cultures grew C. septicum that was sensitive to cephalosporins and aminoglycosides. A postmortem examination showed intense edema of the intestinal wall, air within the mucosa and submucosa, necrosis without inflammatory infiltrate, and extensive bacterial infiltration that affected primarily the terminal ileum and cecum. Air was also observed within the spleen and brain. He had an extensive squamous cell carcinoma of the left lung and renal metastases.

Docetaxel is a new cytotoxic agent that promotes assembly of microtubules and stabilizes them, preventing their depolymerization. Major toxic effects include neutropenia, cutaneous symptoms, and hypersensitivity reactions. In a review article (6), mucositis and diarrhea were observed in 42% and 43%, respectively, of the patients treated with this agent. As far as we know, typhlitis has never been described in association with docetaxel. Three cases of neutropenic enterocolitis have been reported to be associated with the combination of paclitaxel (Taxol) and doxorubicin with both drugs given in a 72-hour infusion (4,5). The evidence of typhlitis was radiological, and all patients recovered without surgery. It was attributed to the combination of deep, although short-lived, neutropenia (that all three patients had) and the direct gut mucosal damage that had potentially been produced by these agents, particularly after having been given as prolonged infusions. The dose level of the drug combination in those patients who developed typhlitis was considered one step above the maximum-tolerated doses in this particular phase I/II study (5). Our patient received docetaxel as a single drug in the currently recommended dose and schedule and developed typhlitis and overwhelming sepsis due to C. septicum infection.

Typhlitis is not a commonly recognized complication of steroid therapy, although many patients who develop typhlitis, such as our patient, are receiving steroids as part of their treatment regimen.

Overwhelming sepsis due to C. septicum in patients with neutropenia is almost always associated with typhlitis (7,8). It has a very poor prognosis, and early medical intervention is necessary to cure some of these patients. Early suspicion of this condition might help to initiate effective antibiotic treatment as soon as possible.

The knowledge that potent new drugs such as docetaxel, which has been associated with early, short, but profound neutropenia, might cause typhlitis is likely to be of use to clinicians who are or may be presented with cancer patients who exhibit abdominal distress signs while receiving chemotherapy.

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Severe Neurotoxicity From Vinorelbine–Paclitaxel Combinations

A recent report (1) indicated enhanced antitumor effects of vinorelbine against murine P388 leukemia when that drug was combined with paclitaxel (Taxol). However, before promoting widespread clinical exploration of the use of these drugs for combination chemotherapy for cancer, we caution that, under some circumstances, this drug combination has the potential to cause severe neurotoxic effects in patients.

Five patients (Table 1) were given a combination of vinorelbine and paclitaxel every other week. After premedication with intravenous dexamethasone, diphenhydramine, and cimetidine, vinorelbine was given intravenously at a dose of 20-30 mg/m² over 30 minutes, followed by a 3-hour intravenous infusion of paclitaxel at a dose of 150 mg/m². All patients had been pretreated with paclitaxel and carboplatin, and one patient, in addition, was also pretreated with cisplatin. Three of five patients were experiencing stable grade 1 (2) sensory neuropathy at the time they began receiving the paclitaxel–vinorelbine combination, while the remaining two exhibited similar but slightly worse neuropathy, classified as grade 2 (2), because they required treatment with analgesics. The three patients with ovarian cancer showed decreasing serum levels of CA-125 marker but had to discontinue therapy because of neurotoxic effects. The other two patients (diagnosed with bronchoalveolar carcinoma and tonsillar cancer) also had no progression of their cancer during treatment. All five patients showed some neurologic improvement after the cessation of paclitaxel/vinorelbine administration.

Vinorelbine tartrate and the taxanes, which are mitotic inhibitors with differing mechanisms and tubulin-binding sites, have shown efficacy against ovarian, breast, non-small-cell lung, and head and neck cancers (3-6). Preclinical (1,7,8) and clinical (9-11) studies support their use in combination with the other. Overlapping toxic effects were not viewed as a deterrent to the use of vinorelbine in combination with other drugs that might cause myelosuppression, since cytokine support might be able to overcome neutropenia. In fact, a pilot study of vinorelbine plus paclitaxel in nine patients with metastatic breast cancer (9) reported grade 3 or 4 neutropenia (2) in all patients and grade 1 or 2 peripheral neuropathy in four. However, a larger study (Hortobagyi G; personal communication) from The University of Texas M. D. Anderson Cancer Center, Houston, reported dose-limiting neurotoxic effects and pelvic pain. Furthermore, Hortobagyi subsequently documented vocal cord paresis and severe motor neuropathy. Another study by Kourousis et al. (10), using a combination of vinorelbine and paclitaxel together with cisplatin, reported that the patients experienced severe neurotoxic effects. Conversely, a study by Fumoleau et al. (11), using combinations of docetaxel and vinorelbine, reported fewer neurotoxic effects than those reported by the Kourousis et al. study.

In patients enrolled in the present study who showed pre-existing sensory neuropathies as a result of earlier treatment with paclitaxel (12), there was onset of severe, relentless, and very slowly reversible motor neuropathy following treatment with vinorelbine plus paclitaxel. All five patients manifested

Table 1. Case histories of paclitaxel-vinorelbine-treated patients

<table>
<thead>
<tr>
<th>Patient age and sex/diagnosis</th>
<th>Prior chemotherapy*</th>
<th>Base-line neuropathy†</th>
<th>Paclitaxel/vinorelbine dose/ mg/m²/course</th>
<th>Outcome/ neurotoxicity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>52-y-old female/ ovarian cancer</td>
<td>Carbo + paclitaxel, 175 mg/m² × 6; DoXIL, 50 mg/m² × 7</td>
<td>Grade 1 sensory</td>
<td>Paclitaxel, 150/every 2 wks × 4; vinorelbine, 20/every 2 wks × 4</td>
<td>Stable; grade 3 sensory; hoarseness</td>
</tr>
<tr>
<td>75-y-old female/ ovarian cancer</td>
<td>Carbo + paclitaxel, 135 mg/m² (24 h) × 6; paclitaxel, 135 mg/m² × 3; DoXIL, 40 mg/m² × 3</td>
<td>Grade 2 sensory</td>
<td>Paclitaxel, 150/every 2 wks × 5; vinorelbine, 25/every 2 wks × 5</td>
<td>Stable; grade 3 sensory; grade 3 motor</td>
</tr>
<tr>
<td>68-y-old female/ ovarian cancer</td>
<td>Cisplatin, 50 mg/m² + doxorubicin, 50 mg/m² + cyclophosphamide, 500 mg/m² × 6; carbo + cyclophosphamide, 600 mg/m²; paclitaxel, 175 mg/m² × 3; paclitaxel, 175 mg/m² × 3; paclitaxel, 225 mg/m² + EMP (900 mg/m² × 3 d) × 8</td>
<td>Grade 1 sensory</td>
<td>Paclitaxel, 150/every 2 wks × 3; vinorelbine, 25/every 2 wks × 3</td>
<td>Negative computed tomograph scan; pelvic pain, slurred speech, paralytic ileus; grade 1 sensory</td>
</tr>
<tr>
<td>72-y-old female/ bronchoalveolar carcinoma</td>
<td>Paclitaxel, 225 mg/m² × 2 every 2 wks × 6; paclitaxel, 200 mg/m² + EMP (900 mg/m² × 3 d) × 4; paclitaxel, 225 mg/m² + carbo × 3</td>
<td>Grade 1 sensory</td>
<td>Paclitaxel, 150/every 2 wks × 2; vinorelbine, 30/every 2 wks × 2</td>
<td>Stable; grade 3 sensory; grade 2 motor</td>
</tr>
<tr>
<td>77-y-old male/ tonsillar cancer</td>
<td>Cyclophosphamide, mechloretamine, doxorubicin (doses unknown over 2 years); DoXIL, 40 mg/m² × 12; paclitaxel, 200 mg/m² × 2 every 2 wks × 3; paclitaxel, 150 mg/m² + carbo × 4</td>
<td>Grade 2 sensory</td>
<td>Paclitaxel, 150/every 2 wks × 2; vinorelbine, 25/every 2 wks × 2</td>
<td>Stable; grade 3 sensory; grade 4 motor</td>
</tr>
</tbody>
</table>

*Carbo = carboplatin, DoXIL = Stealth liposomal doxorubicin, Sequus Pharmaceuticals, Inc., EMP = estramustine phosphate. All paclitaxel regimens were given every 3 weeks and as a 3-hour infusion unless specified. All carboplatin was given with AUC 5 dosing (Calvert formula).
†National Cancer Institute Common Toxicities Criteria.