Anti-Cancer Drugs 2001, **12,** pp. 631–633

Case report

A rare case of advanced ovarian carcinoma who developed difficulty walking 25 days after treatment with weekly paclitaxel

Yoshihiro Kikuchi,[1] Hisakazu Hiramatsu,[2] Hiroshi Seto[2] and Tsunekazu Kita[1]

[1]Department of Obstetrics and Gynecology, National Defense Medical College, Namiki 3-2, Tokorozawa, Saitama 359-8513, Japan. [2]Department of Obstetrics and Gynecology, Seto Hospital, Kanayama 8-6, Tokorozawa, Saitama 359-1128, Japan.

Although taxol has shown significant activity in advanced ovarian cancer, peripheral neuropathy is likely to become the major dose-limiting toxicity. We describe a case of advanced ovarian carcinoma who developed difficulty walking because of marked pain in the lower extremities and loss of proprioception 25 days after treatment with weekly taxol (80 mg/m^2 × 3). [© 2001 Lippincott Williams & Wilkins.]

Key words: Neurotoxicity, paclitaxel, ovarian cancer.

Introduction

Paclitaxel induces a peripheral neuropathy that is characterized by sensory symptoms such as numbness and paresthesia in a glove-and-stocking distribution.[1,2] Symptoms may begin as soon as 24–72 h of the treatment with high doses (more than 250 mg/m^2) but usually occur only after multiple courses at conventional doses (135–250 mg/m^2). Severe neurotoxicity precludes the administration of total doses above 250 mg/m^2 over a period of 3 or 24 h, but severe neurotoxicity is rare at conventional doses (less than 200 mg/m^2), even in patients who have previously received other neurotoxic agents, such as cisplatin.[3]

In this report, we present a rare case of advanced ovarian carcinoma who developed difficulty walking 25 days after treatment with weekly paclitaxel (80 mg/m^2 × 3) in a heavily platinum-pretreated patient.

Correspondence to Y Kikuchi, Department of Obstetrics and Gynecology, National Defense Medical College, Namiki 3-2, Tokorozawa, Saitama 359-8513, Japan.
Tel: (+81) 42 995 1687; Fax: (+81) 42 996 5213;
E-mail: QWL04765@nifty.ne.jp

Case report

A 52-year-old woman (para 3, gravida 4) presented to her local doctor with abdominal swelling and dyspnea. She had neither antecedent peripheral neuropathy nor co-existing medical illness associated with peripheral neuropathy (such as diabetes mellitus and substantial prior alcohol use). A rapidly growing mass in the abdomen and massive pleural effusion with positive malignant cells were detected, and she was referred to our hospital. On 13 October, 1995, she received primary surgery consisting of total simple hysterectomy with bilateral salpingo-oophorectomy and omentectomy. Operative findings showed peritonitis carcinomatosa with diffuse metastases in the peritoneal cavity and massive ascites. Primary tumors, approximately 10–15 cm diameter each, involving both ovaries, ruptured and protruded through the ovarian capsules. Histological examinations revealed serous cystadenocarcinoma (grade 1) with malignant cells in the ascites. She was diagnosed as having stage IV ovarian carcinoma (as defined by the International Federation of Gynecology and Obstetrics). After the primary surgery, CA 125 levels fell to 5784 from 10 304 IU. Because paclitaxel was not available at that time in Japan, treatment with CAP consisting of cyclophosphamide (500 mg/m^2, day 1–3), adriamycin (10 mg/m^2, day 1–3) and cisplatin (50 mg/m^2, day 1) was initiated from 25 October, 1995. Treatment with CAP was performed with 3–4 weeks' interval. After completion of six courses of CAP, CA 125 levels rapidly decreased but she refused second look surgery. Therefore, a further four courses of CAP were added and therafter CA 125 levels fell into the normal range. Chemotherapy was terminated in July 1996. CA 125 levels elevated again 6 months after completion of 10 courses of CAP and reached 549 IU on 24 March,

1997. After completion of an additional five courses with CAP, CA 125 levels decreased to the normal level. After 3 months, CA 125 levels rapidly elevated and pleural effusion reappeared, suggesting resistance to CAP. Thus, treatment with EP consisting of etoposide (50 mg/m^2, day 1–3) and cisplatin (50 mg/m^2, day 1) was initiated on 27 November 1998. After completion of three courses of EP, CA 125 levels rapidly declined but remained in the normal range. After completion of 12 courses of EP, the nadir of CA 125 levels was 235 IU and thereafter exponentially increased to 750 IU. Therefore, we initiated treatment with weekly paclitaxel (80 mg/m^2) using a 1-h infusion schedule. When weekly paclitaxel was administered 3 times, the CA 125 levels rapidly declined to 139 IU. Marked pain in the lower extremities occurred and resulted in difficulty walking 25 days after the last administration of weekly paclitaxel (total 240 mg/m^2). Such difficulty walking continued for about 17 days and myalgia in the lower extremities remained for 39 days. Although all symptoms resolved by 48 days, pleural effusion with elevation of CA 125 appeared and caused dyspnea. Treatment with etoposide (50 mg/m^2, day 1–3) and carboplatin (AUC 5.0) was begun, but was not effective. Thereafter, one course of CAP was added and oral etoposide (25 mg/day) was continued. However, she died of cancer on 17 June 2000.

Discussion

Paclitaxel appears to be one of the most promising antineoplastic agents of the last decade with demonstrated activity in advanced and refractory ovarian, breast, lung, and head and neck cancers. Since paclitaxel administered weekly in heavily pretreated patients with relapsed ovarian cancer has been reported to result in a 30% response rate with a favorable toxicity profile,[4] treatment with weekly paclitaxel to the present patient was performed after heavily pretreatment with cisplatin-based chemotherapy.

Neurotoxicity has been characterized to principally be of mild to moderate severity, even in heavily pretreated patients at paclitaxel doses of 200 mg/m^2 or less. However, some patients have developed a severe sensory motor polyneuropathy at higher doses of paclitaxel (given as a single agent or in combination with cisplatin). Patients with antecedent peripheral neuropathy or co-existing medical illness associated with peripheral neuropathy (such as diabetes mellitus and substantial prior alcohol use) appear to be especially prone to developing peripheral neuropathy. In the present case, neither disease nor prior alcohol use presented, but markedly high total doses (1350 mg/m^2) of cisplatin have been administered so that latent neuropathy may have existed. The neurotoxic manifestations of paclitaxel can be categorized into those resulting from (i) sensory neuropathy, (ii) motor neuropathy, (iii) autonomic neuropathy, (iv) myopathy or myopathic effects and (v) central nervous system effects. In the present case, the neurotoxic manifestations seemed to be mainly myopathy or myopathic effects accompanying sensory neuropathy. Sensory neuropathy may begin as early as 24–72 h after treatment with high single doses, but the neurotoxicity is typically cumulative, with symptoms progressing after such treatment at both high and low doses. The sensory symptoms are generally tolerable. However, paclitaxel treatment may occasionally be disabling, especially in patients treated at taxol doses of 250 mg/m^2 or above or in combination with cisplatin and at low doses in those patients at high risk for developing neurotoxicity[1] (like the present case). Transient myalgias and/or arthralgias are commonly observed after treatment with moderate to high doses of paclitaxel. Large axial muscles, especially shoulder and paraspinal muscles, are frequently involved. Symptoms generally occur 2–3 days after treatment and resolve within 5–6 days. While those symptoms are usually mild and infrequent at paclitaxel doses less than 170 mg/m^2, they become more frequent and severe at paclitaxel doses greater than 200 mg/m^2.[1] Severe muscular complaints occur more often at higher paclitaxel doses (250 mg/m^2 or above). The use of cisplatin in combination with paclitaxel does not appear to affect the severity of myalgias relative to single-agent paclitaxel at comparable doses. The weakness was greater in the lower extremities than in the upper extremities, and patients complained of difficulty with climbing stairs and rising from a low sitting position, like the present case. However, such symptoms as mentioned above suddenly occurred 25 days after treatment with paclitaxel (total doses 240 mg/m^2) and continued for 17 days. Subsequently, further treatment with paclitaxel was precluded and the other treatment was ineffective. Severe neuropathy in the present case occurred 25 days after treatment and is, to our knowledge, the first report. Peterson and Crain[5] have shown that nerve growth factor, a neurotropic factor normally required for maintenance of sympathetic and dorsal root ganglion (DRG) neurons in tissue culture, attenuates the cytotoxic effects of taxol in DRG explant cultures. Such a method that would diminish neurotoxicity might permit the administration of high dose of paclitaxel to heavily cisplatin-pretreated patients, thereby extending the usefulness of this promising agent.

References

1. Rowinsky EK, Eisenhauer EA, Chaudhry V, *et al*. Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol* 1993; **20**(suppl 3): 1–15.
2. Holmes FA, Walters RS, Theriault RL, *et al*. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991; **83**: 1797–805.
3. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; **332**: 1004–14.
4. Fennelly O, Aghajanian C, Shapiro AF, *et al*. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 1997; **15**: 187–92.
5. Peterson E, Crain S. Nerve growth factor attenuates neurotoxic effects of taxol on spinal codeganglion explants from fetal mice. *Science* 1982; **217**: 377–9.

(Received 27 February 2001; accepted 22 May 2001)