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Case report

Use of docetaxel (Taxotere®) in patients with paclitaxel (Taxol®) hypersensitivity

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Anaphylaxis or significant hypersensitivity reaction is one of the most catastrophic potential complications of chemotherapy. There is a 2–5% risk of hypersensitivity with paclitaxel, a commonly used chemotherapeutic agent for various cancers. Three patients, who developed hypersensitivity to paclitaxel infusion, received docetaxel without allergic reactions. Docetaxel may therefore be an alternative treatment for patients with paclitaxel hypersensitivity. [© 2000 Lippincott Williams & Wilkins.]

Key words: Allergic reactions, ovarian neoplasms, taxane.

Introduction

Paclitaxel is the first taxane approved for clinical use. In combination with platinum, paclitaxel has shown significant antineoplastic activity in patients with advanced ovarian carcinoma and is one of the most commonly used chemotherapeutic agents in gynecologic malignancies. Paclitaxel is also effective in platinum-resistant ovarian cancer, breast cancer and non-small cell lung cancer.[1]

Hypersensitivity reactions to paclitaxel, characterized by bronchospasm, hypotension and exanthem, are a major therapeutic challenge.[2,3] Hypersensitivity reactions to paclitaxel have been described for the first time after the initial phase I trials and, since then, several cases have been reported.[4,5] Paclitaxel hypersensitivity reaction usually occurs after initiation of the infusion and is likely due to the release of vasoactive substances, although the precise mechanism is unknown.

We present three patients who tolerated docetaxel despite hypersensitivity reactions after paclitaxel infusion. Hypersensitivity reactions to paclitaxel and treatment alternatives will be discussed.

Case reports

Case 1

A 37-year-old female was diagnosed with stage 2 breast cancer with involvement of three out of 21 axillary lymph nodes. Treatment consisted of a mastectomy followed by radiotherapy and 12 courses of adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Six years later, the patient developed bony metastases and required palliative radiotherapy on the thoracic vertebrae. Since then the disease has been well controlled with hormonal treatments. Two years later, the patient was diagnosed with stage IIIc papillary serous adenocarcinoma of the ovary, and treated with six courses of a combination of cyclophosphamide and cisplatin after tumor-reductive surgery. Four years later, a new bone metastasis in T12 vertebra led to a laminectomy and resection of the tumor mass to prevent spinal cord compression. Surgery was followed by paclitaxel therapy. On the day of paclitaxel administration, the physical examination, the cell blood counts and the serum chemistries were all in normal range. Premedication consisted of oral dexamethasone, 20 mg, 12 and 6 h prior to chemotherapy, and i.v. diphenhydramine (50 mg) plus cimetidine (300 mg) 30 min prior to the infusion of paclitaxel (175 mg/m^2 over 3 h in 1 l of normal saline). A few minutes after the start of the paclitaxel infusion, the patient devel-

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oped a sudden onset of shortness of breath, wheezing, diaphoresis and angioedema with facial flushing and erythematous skin rash. The paclitaxel infusion was immediately stopped, and the patient treated with inhaled albuterol, diphenhydramine and i.v. steroids. These treatments successfully controlled the symptoms and the patient was discharged home. Treatment was later changed to docetaxel (100 mg/m^2 i.v. over 1 h). No anaphylactic reaction occurred.

Case 2

A 50-year-old female was treated for a stage 1 breast cancer by a modified radical mastectomy followed by six courses of adjuvant chemotherapy with 5-fluorouracil, adriamycin and cyclophosphamide (FAC). Seven years later, the patient was diagnosed with epithelial ovarian cancer. Because of the breast cancer history and the presence of bulky disease in the abdomen, the patient was treated with three courses of experimental chemotherapy with high-dose carboplatin chemotherapy (AUC=11) and thrombopoietin support, after signing an informed consent. A near complete clinical remission was obtained and an exploratory laparotomy with interval optimal tumor-reductive surgery performed. Postsurgical chemotherapy was planned with i.v. paclitaxel (135 mg/m^2 over 3 h) followed by carboplatin (AUC=6). The premedication was identical to Case 1. A few minutes into the paclitaxel infusion, the patient developed a sudden onset of shortness of breath, wheezing, diaphoresis, facial swelling and erythematous skin rash. The paclitaxel infusion was stopped. Symptoms were successfully controlled with a bronchodilator, steroid, diphenhydramine and the patient was discharged after a few hours of observation. Docetaxel was then used as an alternative to paclitaxel. Three courses of docetaxel (100 mg/m^2) plus carboplatin (AUC=6) were administered without allergic reactions.

Case 3

A 40-year-old female had optimal tumor-reductive surgery for stage IIIc ovarian cystadenocarcinoma. Six courses of chemotherapy with paclitaxel (175 mg/m^2 over 3 h) and cisplatin (75 mg/m^2) were given postoperatively with no unusual side effects. A second look laparotomy showed no evidence of residual disease. The tumor recurred 2 years later and was treated with eight courses of carboplatin. Because of persistent disease, paclitaxel was administered with the standard premedication (as described above for Case 1). On the third course, the patient developed a mild hypersensitivity reaction manifested by facial swelling and erythematous skin rash shortly after the start of the infusion. The infusion was immediately stopped and the reaction subsided. Despite additional treatments including liposomal adriamycin (Doxil®), topotecan and gemcitabine, the tumor progressed. Because of the good initial response to paclitaxel, the patient was then rechallenged with this drug. An i.v. premedication consisting of dexamethasone 20 mg every 6 h, cimetidine 300 mg every 8 h and diphenhydramine 25 mg every 6 h was administered for 24 h, after which the paclitaxel infusion was started. Approximately 15 min into the infusion, the patient complained of urticaria. The infusion was stopped. The urticaria was successfully controlled with i.v. dexamethasone and diphenhydramine, and the patient uneventfully discharged after 24 h of observation. Subsequently, docetaxel (100 mg/m^2) was administered without allergic reactions.

Discussion

Paclitaxel hypersensitivity reactions can be mild, as manifested by facial flushing and skin rashes, or severe as manifested by dyspnea, bronchospasm, urticaria and hypotension. Severe hypersensitivity reactions to paclitaxel were observed during phase I investigations. An early series reported that 32 of 301 patients treated with paclitaxel experienced hypersensitivity reactions; 41% of these occurred despite prophylactic premedication with steroids and antihistamines (incidence with premedication=4.36%).[6] The current standard premedication for paclitaxel consists of oral dexamethasone, 20 mg, 12 and 6 h before the treatment, and infusion of diphenhydramine 50 mg plus cimetidine 300 mg (or ranitidine 50 mg) prior to chemotherapy administration.[3] The common practice of this premedication has led to a decreased incidence of significant hypersensitivity reactions from 10 to 2%. Recently, in two phase I/II trials in previously untreated patients with either lung or ovarian cancers, a single infusion of dexamethasone 10–20 mg, diphenhydramine 50 mg and cimetidine 300 mg 30 min before paclitaxel infusion was demonstrated safe and more convenient than the standard premedication.[7]

The precise mechanisms for the hypersensitivity reactions remain unclear. Various reports suggest that the vehicle, Cremophor EL, is the causative agent.[8] However, in a study of nine children treated with VM-26 dissolved in Cremophor EL, the basophilic hista-

Table 1. Prophylaxis of taxane hypersensitivity reactions

Drug	Dexamethasone	Diphenhydramine	Cimetidine[a]
Taxol	20 mg orally 12 and 6 h prior to Taxol	50 mg i.v. 30 min prior to Taxol	300 mg i.v. 30 min prior to Taxol
Taxotere	8 mg orally every 12 h for 3 days starting 24 h prior to Taxotere	50 mg i.v. 30 min prior to Taxotere	none

[a]Alternatively, i.v. famotidine 20 mg or ranitidine 50 mg can be used 30 min before chemotherapy.

mine release occurred only with the active drug and not with the vehicle alone.[9] These immunologic studies should be performed for paclitaxel as well. In any case, a severe paclitaxel hypersensitivity reaction despite premedication is usually a contraindication for further use, although further administration of paclitaxel may be possible following desensitization. Desensitization may be accomplished by infusion of successive decreasing dilutions of paclitaxel (starting at 1:100 000).[10,11]

Despite the premedication and the desensitization procedures, significant hypersensitivity reactions may still occur. Therefore, substitution of paclitaxel with docetaxel has been suggested.[12] Two of the cases we described had a significant hypersensitivity reaction to paclitaxel accompanied by a sudden onset of respiratory distress, and one had a milder reaction with facial flushing and generalized urticaria without dyspnea. All three patients were given docetaxel, which they tolerated without any evidence of hypersensitivity reaction. Docetaxel premedication consisted of oral dexamethasone 8 mg every 12 h for 3–5 days, starting 24 h prior to docetaxel administration, and i.v. diphenhydramine 50 mg 30 min prior to docetaxel. Lokich *et al*. reported a similar tolerance of docetaxel in four patients with paclitaxel hypersensitivity.[13]

Although hypersensitivity reactions have also been reported for docetaxel,[15] paclitaxel and docetaxel do not seem to have overlapping hypersensitivity mechanisms. We recommend the use of a standard premedication before paclitaxel and docetaxel (Table 1). The attending physician should consider withdrawal of β-blockers, if indicated, to prevent bronchospasm. If hypersensitivity develops during paclitaxel infusion, treatment needs to be interrupted and supportive care administered. Frequently, paclitaxel can be resumed on the same day at a slower pace under very close monitoring of vital signs. The use of ephedrine sulphate 25 mg orally 1 h before chemotherapy should be considered, unless the patient has unstable angina or hypertension. For patients with persistent reactions, paclitaxel should be discontinued. Desensitization procedures in a controlled environment (i.e. intensive care) may also be tried.[11] However, if the use of a taxane is considered an important part of the patients' treatment, we recommend considering docetaxel in lieu of paclitaxel since hypersensitivity cross-reactions have not been reported to date.

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