Abstract

Aim This study was a retrospective analysis of our experience with severe cross-hypersensitivity reactions (HSR) to the taxanes paclitaxel (P) and docetaxel (D) in patients with breast cancer.

Patients and methods We evaluated patients with breast cancer treated with P or D who experienced severe HSR to one of the two taxanes. Severe HSR was defined as any reaction severe enough to warrant discontinuation of the drug. Initial intravenous premedication for paclitaxel was dexamethasone (20 mg), ranitidine (50 mg) and dexchlorpheniramine (10 mg). For docetaxel, dexamethasone (4 mg) orally every 12 hours was administered the day before infusion and dexamethasone (20 mg) was administered intravenously prior to infusion. After severe HSR to the taxane and 30 minutes before infusion of another taxane, we administered dexamethasone (4 mg) orally every 12 hours was administered the day before infusion and dexamethasone (20 mg) was administered intravenously prior to infusion. After severe HSR to the taxane and 30 minutes before infusion of another taxane, we administered dexamethasone (20 mg), ranitidine (50 mg) and dexchlorpheniramine (10 mg) iv as a premedication, and we also increased the time of the infusion.

Results Between March 2009 and April 2010, 23 patients experienced an initial severe HSR to taxane (12 P, 11 D). Substitution of another taxane was conducted in 17 patients in the two weeks following the initial HSR. Eight patients had an initial HSR with P, and three had a cross-HSR to D. Nine patients had an initial HSR to D, and four of these patients had a cross-HSR to P. Among the 17 patients who received both taxanes, 7 (41%) had a cross-HSR. All cross- HSRs were sufficiently severe (grade 3–4) to suspend taxane treatment permanently. In the remaining 6 patients, a desensitisation protocol to taxanes was performed by increasing the dose of the diluted drug (4 P, 2 D), which resulted in administration of the drug without complications in all cases. There were no treatment-related deaths.

Conclusion Severe cross-HSR between P and D occurred in a significant proportion of our patients with breast cancer, so care must be taken when substituting taxanes (paclitaxel and docetaxel). A desensitisation protocol can be an effective alternative to decrease the risk of a new HSR.

Keywords Paclitaxel · Docetaxel · Cross-resistance · Hypersensitivity reaction · Cross-reaction

Introduction

Taxanes are among the most widely used chemotherapies in the treatment of various types of tumours, including breast cancer [1]. Side effects include hypersensitivity reactions (HSR) that may limit their use.

The habitual use of premedication regimens with corticosteroids and antihistamines has decreased the incidence of HSR to taxanes, but the incidence remains between 2 and 5%. Such reactions may endanger patients’ lives.

The exact mechanism of HSR to taxanes is unknown and probably multifactorial. It is not clear if the reaction to paclitaxel is induced by paclitaxel itself or is secondary to the diluent Cremophor EL. Docetaxel uses an excipient, polysorbate 80, that is different from the excipient in paclitaxel.

HSR to taxanes usually occur during the first few minutes of the first or second infusion of the drug (56% occur during the first infusion). Clinically, HSR often present with systemic signs and symptoms (dyspnoea, oropharyngeal pressure sensation, back pain, rash, hyperthermia, tachycardia and occasional feelings of impending doom)
but usually improves rapidly after discontinuation of the infusion and administration of systematic medication [2]. When HSR occur and the taxanes are necessary for treatment, substitution of taxanes with similar efficacy (paclitaxel with docetaxel or docetaxel with paclitaxel) is possible. However, the risk of cross-HSR to taxanes has been poorly evaluated.

In this study, we analysed our experience with severe cross-HSR between the taxanes paclitaxel and docetaxel in our patients with breast cancer.

Material and methods

Study design

We evaluated patients with breast cancer treated with paclitaxel or docetaxel who experienced a severe HSR to one of the two taxanes. A severe HSR was defined as any reaction severe enough to warrant discontinuation of the drug. Data collected included the age of the patient, stage of the tumour, histological diagnosis and date of treatment.

The initial intravenous premedication for paclitaxel was dexamethasone 20 mg, ranitidine 50 mg and dexchlorpheniramine 10 mg. The initial intravenous premedication for docetaxel was dexamethasone (20 mg) on the day of infusion and dexamethasone (8 mg) orally every 12 h the day before infusion. After a severe HSR to a taxane and 30 min before the administration of another taxane, we administered dexamethasone (20 mg), ranitidine (50 mg) and dexchlorpheniramine (10 mg) iv as a premedication, and we increased the time of the infusion.

The desensitisation protocol to taxanes was as follows: (i) premedication the day before treatment: montelukast (10 mg) once a day, dexchlorpheniramine (6 mg) at night, ranitidine (300 mg) at night and methylprednisone (120 mg) (1-0-1); (ii) premedication the day of treatment: montelukast (10 mg) on the morning of treatment and dexchlorpheniramine (10 mg) iv, dexamethasone (20 mg) iv, ranitidine (50 mg) iv and ondansetron (8 mg) iv 30 min before the taxane; and (iii) for the taxane administration, we used a protocol with three taxanes solutions (A, B, C) in increasing concentrations (1/100, 1/10, 1 of the total dose) in 12 steps (4 with each solution) at 10–15 minute intervals, with increasing rates of infusion from a minimum low dose (1/10,000 to 1/1,000), until the therapeutic dose was reached. In the last step, the concentration and infusion rates were similar to those used in a non-sensitised patient. Patients were monitored during the process to treat possible reactions that could occur and the infusion rate was adjusted to patient tolerance.

Results

Between March 2009 and April 2010, 23 patients had a severe HSR to paclitaxel or docetaxel (12 P, 11 D). The patients’ characteristics are described in Table 1. Substitution with the other taxane was conducted in 17 patients 2 weeks after the initial HSR.

Eight patients had an initial HSR with P; 3 of these patients had a cross-HSR to D. Nine patients had an initial HSR to D; 4 of these patients had a cross-HSR to P. Among the 17 patients who received both taxanes, 7 (41%) had a cross-HSR. All cross-HSRs were strong enough (grade 3–4) to warrant discontinuation of the taxane. In the remaining 6 patients, a desensitisation protocol to taxanes was performed by applying dilutions with increasing doses of the drug (4 P, 2 D) until the drug could be administered without complications in all cases. There were no treatment-related deaths.

Discussion

Severe HSR may limit the use of taxanes as an efficient treatment in patients with breast cancer and may even endanger their lives. In our study, 41% of patients had cross-HSRs between the two taxanes that were of sufficient severity (grade 3–4) to permanently discontinue treatment, despite adequate premedication and prolonged infusion time.

The solvents of paclitaxel and docetaxel are different (Cremophor EL and polysorbate 80, respectively), and HSR occurred with both taxanes. It is possible that there is a group of patients who are allergic to the paclitaxel solvent, Cremophor EL, but there could also be another group with an allergy to the taxane molecule instead of the solvent [3].

Currently there are very few data on the risk of cross-HSR to taxanes. The published experience is limited to case reports and small or retrospective studies. Two reports with a total of seven patients with HSR to paclitaxel described well-tolerated use of docetaxel, which may be a safe alternative to paclitaxel [4, 5]. In contrast, Denman et al. [6] presented a patient with severe HSR to docetaxel after previous HSR to paclitaxel. Dizon et al. [3] performed a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
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<tr>
<td>Age (years)</td>
<td>Median 45 (28–70)</td>
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<tr>
<td>Tumour stage</td>
<td>Early 8 (65%), Advanced 15 (65%)</td>
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<tr>
<td>HSR</td>
<td>Paclitaxel 12 (62%), Docetaxel 11 (48%)</td>
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<tr>
<td>Number of infusions to initial HSR</td>
<td>First 14 (61%), Second 13 (63%), Third 2 (9%)</td>
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