

Hypersensitivity Reactions to Docetaxel: Retrospective Evaluation and Development of a Desensitization Protocol

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Key Words

Desensitization · Docetaxel · Hypersensitivity reactions · Lung cancer

Abstract

Background: Docetaxel (DT) is an extensively used taxane, frequently associated with hypersensitivity reactions. The aim of this study was to record the epidemiological and clinical features of hypersensitivity to DT in non-small cell lung cancer patients in order to obtain useful information concerning the management of these patients. We also developed a desensitization protocol and evaluated its clinical application. **Methods:** We retrospectively reviewed records of 620 non-small cell lung cancer patients treated with DT-containing regimens in the adjuvant, first-, second- or next-line setting. Data from 102 patients who had exhibited hypersensitivity reactions were analyzed according to the Common Toxicity Criteria for Adverse Events version 3.0. Five patients were chosen for the desensitization protocol. We applied the standard protocol for parenteral desensitization to β -lactam antibiotics, and DT treatment was carried out with a series of 10-fold dilutions in sufficient volume to administer the total dose. **Results:** One hundred and two patients (16.5%) were recorded as having hypersensitivity to DT. Reactions were

observed after approximately 2.5 ± 1.0 cycles. Only 14 patients (14/620, 2%) developed grade 3–4 hypersensitivity. Reactions were more likely in patients during second- or third-line chemotherapy, but no other correlation (age, gender, atopic status) was observed. Five patients completed a parenteral desensitization protocol and continued their treatment uneventfully. **Conclusions:** Hypersensitivity reactions to DT respond quickly to discontinuation along with appropriate supportive care. Premedication and increased infusion time may allow readministration. The desensitization protocol that we developed provides a reliable alternative to permanent discontinuation of DT.

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Introduction

Hypersensitivity is defined as an unexpected reaction that cannot be explained by the known toxicity profile of a chemotherapeutic agent [1]. Hypersensitivity reactions (HSR) have been observed during the use of many antineoplastic agents, including taxanes, asparaginase, epipodophyllotoxins, procarbazine, doxorubicin, 6-mercaptopurine and monoclonal antibodies (cetuximab, trastuzumab, rituximab and bevacizumab) [1]. In many clinical

trials, HSR are considered as a minor side effect of the antineoplastic treatment and are under-reported. There also seems to be an inconsistency in terminology, grading and management of these events. Nevertheless, they frequently cause considerable discomfort and often result in the discontinuation of a potentially beneficial treatment [1–3]. This led to the development of desensitization protocols for a number of chemotherapy agents and monoclonal antibodies [4, 5].

Taxanes – paclitaxel and semisynthetic docetaxel (DT) – are approved as first-line treatment for non-small cell lung cancer (NSCLC) [6, 7], breast [8, 9] and ovarian [10] carcinomas and are also used in the treatment of numerous other malignancies [11–15]. Paclitaxel is a natural alkaloid isolated from *Taxus brevifolia*, whereas DT is a semi-synthetic compound produced from 10-deacetyl-baccatin III found in *Taxus baccata* [16]. In earlier studies, hypersensitivity associated with taxanes was observed in as high as 42% of patients treated, and 2% of these reactions were severe [17]. Most DT-associated HSR (95%) occur during the first or second infusion [6, 18], and in some cases, it only takes 1 mg of DT for HSR to develop [19, 20]. Symptoms include dyspnea or bronchospasm (81%), urticaria, flushing (74%), hypotension and angioedema [21, 22]. Sudden death may occur [19]. Although these symptoms are suggestive of an IgE-mediated mechanism, there is usually no history of previous exposure and sensitization, as is required in a type I allergic reaction. Therefore, the most likely mechanism seems to be direct mast cell degranulation, compatible with anaphylactoid reactions (non-IgE mediated) [1, 2, 23].

The aim of this study was to record the epidemiological and clinical features of HSR to DT in NSCLC patients treated with this agent in order to obtain some useful clinical information for the management of patients receiving DT infusion. In addition, we developed a desensitization protocol and evaluated its clinical application.

Material and Methods

We retrospectively analyzed the records of 620 taxane-naïve NSCLC patients consecutively treated with DT-based regimens at the Oncology Department of Sotiria General Hospital during the years 2001–2008. We studied the treatment they had received and recorded the patients who had exhibited hypersensitivity. These reports were analyzed according to the Common Toxicity Criteria for Adverse Events version 3.0 [24], and their characteristics and management were also recorded. All data were collected on a SPSS 11.5 database. Skin tests (prick and intradermal) were not performed because DT is considered to be toxic when in touch with

Table 1. Characteristics of the 102 patients who had been recorded as ‘allergic’ to DT

Age, years	mean	69.7
	range	37–77
Sex	male	94 (92.1)
	female	8 (7.8)
Cycle of chemotherapy	mean	2.5
	range	1–5
	median	2
Line of chemotherapy	adjuvant	3 (3)
	first line	22 (22)
	≥second line	77 (75)

Figures in parentheses are percentages.

the skin [25, 26]. However, prick tests with late readings after 24 h have been reported in the past without toxicity [27].

In patients with recently recorded hypersensitivity, we decided to implement a desensitization protocol which was based on the standard protocol for parenteral desensitization to β-lactam antibiotics with some minor modifications, as has been used in chemotherapy HSR in the past as well [28]. DT treatment was carried out with a series of 10-fold dilutions (up to 1:100,000) in sufficient volume to administer the total dose. The patients’ blood pressure, heart rate and oxygen saturation were monitored every 15 min [28]. Intramuscular epinephrine (1:1,000), diphenhydramine and methylprednisolone were placed at the bedside. The possibility of intubation was available on-call, if needed, and the allergist was on site to answer questions regarding the desensitization and to modify the protocol. Desensitization was completed within 8 h and was performed at an outpatient setting. Each patient who was submitted to desensitization had been fully informed and had signed a consent form. This protocol was approved by the appropriate hospital ethics committee.

Results

Among the total of 620 patients, 36 patients (5.8%) had received adjuvant treatment, 257 (41.5%) had undergone first-line treatment for locally advanced or metastatic disease and 327 patients (52.7%) had received chemotherapy as second- or next-line treatment. HSR had been reported in 102 out of all 620 patients (16.5%).

The characteristics of these 102 patients, recorded as having an allergic reaction to DT, are shown in table 1. According to our findings, HSR were recorded after a median number of 2 cycles (range 1–5). Only 14 out of 620 patients (2%) developed grade 3–4 HSR. Patients who received second- or next-line chemotherapy and who had been receiving other cytotoxic agents in the past were

Table 2. Frequency of clinical symptoms of DT-related hypersensitivity in 102 patients

Facial flushing	82 (80)
Chest discomfort/pain	68 (67)
Back pain	52 (51)
Tachycardia	46 (45)
Erythematous rash	37 (36)
Hypotension	25 (25)
Pruritis/urticaria	20 (20)
Facial swelling	18 (18)

Figures in parentheses are percentages.

Table 3. Protocol of desensitization to DT

Solution, mg/ml	Volume, ml	Dose, mg
0.00001	1	0.00001
0.0001	1	0.0001
0.001	1	0.001
0.01	1	0.01
0.1	1	0.1
1	1	1
1	2	2
1	4	4
10	0.8	8
10	1.6	16
10	3.2	32
10	3.5	35
10	6.4	64

more likely to develop HSR, as compared to chemotherapy-naïve patients ($p < 0.01$). The patients' gender, age, site of primary tumor, histological type, degree of differentiation, stage at diagnosis and number and sites of metastatic lesions did not correlate with the development of HSR. Moreover, the presence of comorbidities (medical history of diabetes mellitus, chronic obstructive pulmonary disease, hypertension and coronary artery disease) was not associated with the development of HSR to DT.

Atopic status of patients who had exhibited DT-associated HSR was evaluated by the presence of a positive skin prick test to 1 or more common environmental aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, *Alternaria alternata*, *Cladosporium*, *Aspergillus fumigatus*, grass mix, *Olea europaea* pollen, *Parietaria officinalis* pollen and latex; ALK Company). The presence of atopic disease or positive skin

prick test did not correlate with the development of HSR to DT.

The various presentations of HSR are summarized in table 2. Patients most commonly developed facial flushing, back pain, chest discomfort, tachycardia, erythematous rash and pruritus.

With regard to management, DT rechallenge had been performed in 43 out of 88 patients (49%) with grade 1–2 HSR. Readministration had not been attempted in the rest of the patients for the following reasons: therapeutic availability of other DT-free chemotherapy schemes (27 patients), patients' noncompliance (7 patients) and completion of chemotherapy without the substitution of DT (11 patients). The 43 patients who were rechallenged received the following premedication: ranitidine 150 mg, methylprednisolone 1 mg/kg (maximum 60 mg) and cetirizine 10 mg 13, 7 and 1 h before DT administration, and rechallenge was performed 1 week after the initial HSR. Only 27/43 (63%) of the patients successfully completed their DT-containing treatment. The remaining 16/43 (37%) developed HSR despite the premedication.

Desensitization was implemented in 5 patients who had known DT hypersensitivity. The desensitization protocol was performed either because there was no alternative therapeutic solution besides DT (2 patients) or because the patient insisted on trying all possible methods to receive this drug (3 patients). Table 3 demonstrates the dilutions and total dose in 1 patient. All 5 patients completed the parenteral desensitization protocol with success and were able to continue their treatment until completion, with the same protocol of desensitization performed each time uneventfully.

Discussion

The incidence of HSR to DT is rising owing to its growing clinical use in various malignancies, such as NSCLC, head and neck, breast, prostate and gastric carcinoma. HSR following DT exposure may develop within minutes after the beginning of the infusion and at any time within a cycle of therapy. Risk factors examined in our study were chosen based on factors previously found to be correlated with HSR to other chemotherapy agents. There were no data available on eosinophilia or total IgE levels.

In our study, HSR (anaphylactoid and IgE mediated) appeared in 16% of the patients studied (2% were severe grade 3–4 HSR) after a median of 2 cycles of chemother-

apy – findings that agree with the literature [19, 29, 30]. According to our results, clinical and pathological parameters of the patients did not correlate with the development of HSR. The predominance of males among patients who exhibited HSR is in accordance with the gender differences observed in the total of 620 NSCLC. This reflects the Greek epidemiology of NSCLC patients, probably as a consequence of gender-specific smoking behavior. Our statistical analysis did not prove gender to be a risk factor for the development of HSR. With regard to the line of treatment, patients in second-line chemotherapy are more prone to develop HSR. The higher incidence in this group of patients may be attributed to immunological stimulation caused by the chemotherapy drugs used in the adjuvant and first-line setting, rendering patients more susceptible to drug hypersensitivity, i.e. by exposure to common drug excipients. These differences may also be associated with the frequency of DT use in each line of treatment.

Paclitaxel-associated HSR may be attributed to the drug's excipient, Cremophor EL, a nonionic polyoxyethylated castor oil added to solubilize the drug (527 mg in each milliliter of paclitaxel solution). This substance has been shown to trigger histamine release and hypotension in dogs. It has also been proven to induce the formation of needle-like structures and micelles that cause complement activation leading to anaphylactic-like reactions [1, 2, 23]. Nevertheless, since DT is also associated with HSR but does not contain Cremophor EL, it is likely that the taxane moiety is the main etiologic agent responsible for these reactions [31].

Even though the pathophysiology of HSR to DT is unclear, several mechanisms have been proposed [25].

Sometimes these reactions may develop after multiple infusions, suggesting the need for sensitization. These can be described as type I allergic reactions, which result from the degranulation of mast cells and basophils following IgE binding. Histamine and other cytokines (leukotrienes, prostaglandins), which have prominent inflammatory potential, are then released, leading to the constriction of the smooth muscles and the dilation of capillaries. Early onset of symptoms during DT administration further supports the above explanation [32]. Both type II complement-mediated killer cells activated reactions (manifesting with thrombocytopenia, hemolysis and Evans syndrome) and type III delayed reactions (urticarial vasculitis) may also be observed during DT administration [33].

Premedication does not eliminate the risk of HSR [34, 35], and some protocols have been reported offering desensitization to DT [19, 36, 37]. In our study, premedication was successful in only 63% of patients who had DT-related hypersensitivity, while the application of a desensitization protocol was successful in all 5 patients.

In conclusion, although HSR are common with the use of DT therapy, serious, life-threatening reactions only account for 2.2% of all HSR. They respond quickly to the discontinuation of the drug and to appropriate supportive care. Premedication with steroids and antihistamines as well as an increase in infusion time may allow readministration of the drug to some individuals. The desensitization protocol that we developed provides a reliable alternative to permanent DT discontinuation. Larger trials should be conducted in the future in order to prove its usefulness in everyday clinical practice.

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