Non-allergic nature of docetaxel-induced acute hypersensitivity reactions

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Based on observations of a discrepancy between 'hypersensitivity' reactions to docetaxel (DT) and the clinical features of allergic reactions, we explored the hypothesis that DT-induced acute hypersensitivity reactions (AHRs) have a non-allergic origin. Forty cancer patients receiving DT and 16 patients receiving other potentially allergenic chemotherapeutic agents were included in the study. All DT patients received standard pre- and post-medication. Before, during and after administration of the drugs, clinical symptoms and signs were recorded, and serial blood sampling was performed for the first 2 cycles for all patients or in all subsequent cycles in case of AHRs. Plasma histamine and serum tryptase, two established drug allergy markers, were measured. Seventy-five chemotherapy sessions were evaluable. Nine patients on DT, two on paclitaxel (PT) and one on pegylated doxorubicin experienced an AHR during the first course of chemotherapy. In all cases, heart rate remained stable or increased, while arterial pressure was unchanged or raised; no hypotension or bradycardia was noted. All episodes resolved with discontinuation of drug and did not reappear during a re-challenge with the same agent 30 min later. Tryptase levels were normal in all pre- and post-exposure samples (post-exposure: 11.32 ± 35.63 μg/l, normal values <13.5 μg/l). In all but one AHR-free PT, pre- and post-exposure histamine concentrations remained normal (post-exposure: 2.86 ± 11.88 nM, normal values <10 nM). No eosinophilia or basophilia was observed. We conclude that 'hypersensitivity' reactions to DT seem not to be histamine or tryptase mediated; thus, their allergenic nature should be questioned. The underlying mechanism may be related to other biological processes such as the release of vasoactive molecules or non-histamine/tryptase-mediated allergy. If the former is demonstrated by further study, the safety of DT administration will be confirmed, and the pre- and post-medication practice might be revisited.
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Introduction

The semisynthetic taxoid docetaxel (DT) has emerged as a highly active agent against a variety of malignancies [1–3]. Main toxicities include myelosupression, cutaneous reactions and cumulative-dose fluid retention syndrome. Acute hypersensitivity reactions (AHRs) are experienced by some patients, and although rarely, if at all, fatal, they induce distress in patients as well as treating physicians and nurses. The etiology of AHRs remains unclear although they have been attributed either to the DT molecule being extracted from the needles of the European Yew tree (*Taxus baccata*) or the polysorbate 80 in the diluent [1,2].

Phase I trials have reported infusion-related hypersensitivity reactions and cutaneous reactions in 13% of patients, particularly associated with shorter-infusion schedules, but with only a few severe reactions [1–3]. Phase II trials have reported AHRs in 31% of patients, of which 7% were severe, although only 0.5% of patients had to discontinue therapy [3,4]. According to several reports, a typical AHR is associated with flushing, a mild or acute rash, pruritus, fever, dyspnea, chest or epigastric or back constrictive pain [1–5].

Pre-medication with various agents, including mostly H_1- and H_2-blocking agents along with corticosteroids, has been evaluated as a way to decrease the incidence of AHRs with conflicting results. An EORTC study showed that although pre-medication may be needed in order to reduce the incidence of AHRs, there were no clear recommendations on the precise benefit or best pre-medication schedule [4,5]. Currently, common practice of co-medication for both DT and PT consists of dexamethasone, cimetidine and diphenhydramine or their equivalents, starting 12 h before drug infusion, with glucorticoids orally administered for 48–72 h post-infusion. Moreover, when an AHR occurs, it is always considered and treated as a true histamine-mediated allergic reaction (anaphylactoid), in spite of the lack of

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clinical or laboratory evidence of such an underlying mechanism.

We were prompted to conduct the present study by the apparent discrepancies between the characteristics of AHRs to DT and the classic features of allergic, histamine-mediated drug reactions [6]. Although in allergic reactions, an initial exposure to the drug should be uneventful and subsequent courses should present with reactions, this is not the case for DT, where AHRs usually occur in the first and less often and rarely in the second and third cycles, respectively, and further subsiding thereafter. In addition, our and others' clinical observations suggest that DT AHRs have some dose and flow rate dependency, particularly in the rare case of an accidental administration of a more rapid drug infusion. Finally, although severe hypotension is an almost universal feature of anaphylactoid reactions, our experience with the routine administration of DT shows that during AHRs hypertension is the rule. All the aforementioned clinical data are suggestive of a vasomotor rather than an anaphylactic reaction to DT administration. These observations led us to study the underlying mechanism of AHRs, in order to better prevent and manage them, given the eventual short-, mid- and long-term side-effects of aggressive anti-anaphylaxis treatment.

Patients and methods

Fifty-six consecutive patients suffering from various solid tumors and no other diseases (particularly immunologic disorders) were enrolled in the study. Forty patients were treated with DT, whereas another 16 received other potentially allergenic chemotherapeutic agents such as paclitaxel (PT), pegylated doxorubicin, gemcitabine and adriamycin ($n = 6$, 5, 4 and 1, respectively), and served as the control group. All DT and PT patients received standard pre- and post-medication according to common practice (either 16 mg p.o. methylprednisolone 12, 6 and 1 h before and 2, 10, 22 and 36 h post-DT infusion or 8 mg i.v. dexamethasone 12 and 6 h before PT infusion, as well as H_1 and H_2 blockers starting 12 h before infusion, see Table 1).

Before, during and after administration of the drug, clinical symptoms and signs were recorded, whereas serial blood sampling was performed just before, as well as 15, 30 and 60 min post-infusion. These procedures were repeated for the first two courses of therapy and thereafter only in cases of an AHR in the first or second course. A complete blood count was performed on every patient before and after chemotherapy infusion.

Table 1 Treatment

Chemotherapeutic	DT	PT	LD	GC	ADR
N (patients)	40	6	5	4	1
Dose (mg/m^2)	100	175	50	1000	50
Pre-medication	yes	yes	no	no	no
Post-medication	yes	yes	no	no	no
Antiemetics	no	no	5-HT_3/dex	5-HT_3/dex	5-HT_3/dex

DT: docetaxel, PT: paclitaxel, LD: liposomal doxorubicin, GC: gemcitabine, ADR: adriamycin, 5-HT_3: serotonin antagonists, dex: dexamethasone.

In order to evaluate the biochemical response associated with an AHR, we selected plasma histamine and serum tryptase, both considered specific markers of drug allergy [7,8]. Histamine, a major mediator of anaphylaxis is released primarily by mast cells into the systemic circulation after allergic stimuli, with a plasma half-life of up to 30 min [7,8]. Tryptase is a neutral protease stored in mast cell granules and released into the circulation after systemic mast cell activation. It is virtually absent from normal serum, thus making this marker more specific and reliable of anaphylaxis. Its serum half-life is between 60 and 120 min [7,8].

Blood was drawn from a peripheral vein and separately processed for histamine and tryptase measurements. (i) Histamine specimens were collected in EDTA-containing tubes that were promptly centrifuged at 4°C, 1500 r.p.m. for 3 min; plasma was frozen at −20°C. Specimens were carefully inspected for hemolysis, as the presence of histamine in circulating normal basophils may give false-positive results. A commercial RIA kit (Immunotech, Coulter, France) was used to determine plasma histamine concentrations. The lower limit of detection of the assay was 0.2 nM, whereas the normal values of histamine are below 10 nM. Anaphylactic reactions are associated with above 10 nM plasma concentrations. (ii) Blood samples for tryptase measurements were collected in glass tubes and centrifuged similarly to histamine samples. Extracted serum was also stored at −20°C. A commercially available fluoro-enzyme-immunometric assay (UniCAP; Pharmacia & Upjohn Diagnostics, Upssala, Sweden) was used with a lower limit of detection of below 1.0 μg/l. According to data from the kit's manufacturer, normal levels of serum tryptase do not exceed 13.5 μg/l; however, as some normal individuals have values above 13.5 μg/l, we considered 15 μg/l as the higher normal tryptase concentration in serum.

All RIA experiments were performed in duplicate. Plasma histamine was measured in baseline samples as well as in those drawn 30 min after, whereas serum tryptase was measured at baseline and at 60 min, according to their half-lives.

Statistics

Descriptive data were expressed as mean ± SD. Linear regression analysis was used to assess the relationship between the selected variables, whereas Student's *t*-test was used to analyze difference between means in each group. Statistical significance was taken as $p < 0.05$. All statistical analyses were performed using SPSS version 10.0 software.

Results

Patient characteristics are shown in Table 2. A total of 75 chemotherapy courses were evaluable. In 19 (25.3%) patients, some type of reaction was associated with treatment, whereas in the remaining patients, infusions were uneventful. Thirteen (23.2%) of the enrolled patients experienced an AHR: nine in the first course only, three in the second course only and one in all subsequent courses. The overall AHR incidence in DT-treated patients was 22.5% (nine patients), whereas two patients receiving PT and one receiving pegylated doxorubicin experienced an AHR.

The AHRs consisted of, in decreasing order of frequency, head flushing, severe epigastric pain, severe back pain, hypertension, tachycardia, dyspnea, chest pain, bronchospasm or some combination of the above (Table 3). No hypotension or bradycardia was noted. All reactions subsided soon after discontinuation of the infusion and did not reappear after re-challenge 15–30 min later with a lower infusion rate without any additional treatment, with the exception of one woman in the DT group who presented another reaction upon re-challenge, but finally tolerated the infusion well (interestingly, this patient presented with the same response in all DT courses).

Table 2 Patient characteristics

N	56
Age (mean ± SEM, years)	54.6 ± 12.7
Sex (female/male)	41/15
Site of solid organ tumor (%)	
breast	56
lung	24
ovarian	7
tongue	2
sarcoma	2
melanoma	7
stomach	2

Table 3 Type of reaction

Symptom or sign	Frequency (%)
Head/neck flushing	13 (17.3)
Epigastric pain	8 (10.7)
Back pain	7 (9.3)
Hypertension	6 (8)
Tachycardia	5 (6.7)
Dyspnea	5 (6.7)
Chest pain	4 (5.3)
Bronchospasm	1 (1.3)
Combination of the above	12 (16)

Table 4 Histamine and tryptase levels at baseline and at their half-lives

Biochemical marker	0 min	30 min	60 min	*p*
Histamine (nM)	1.249 ± 0.87	2.863 ± 11.88		NS
Tryptase (μg/l)		10.956 ± 34.97	11.322 ± 35.63	NS

Table 5 Histamine and tryptase levels in event-free and AHR courses of chemotherapy

Biochemical marker	AHR-free	AHR	*p*
Histamine 0 min (nM)	1.383 ± 0.96	0.914 ± 0.48	NS
Histamine 30 min (nM)	3.311 ± 13.85	1.623 ± 1.71	NS
Tryptase 0 min (μg/l)	13.33 ± 40.42	4.131 ± 2.387	NS
Tryptase 60 min (μg/l)	14.105 ± 41.86	4.28 ± 2.64	NS

Laboratory assessments

Blood eosinophil and basophil counts were normal in all cases (137 ± 190 and 37 ± 80, respectively) before and 10–12 h post-infusion.

Plasma histamine concentrations remained below those reported for anaphylaxis in all but one AHR-free patient. There was no statistically significant increase in histamine concentrations at 30 min compared to baseline levels, (1.249 ± 0.874 and 2.863 ± 11.883 nM at baseline and 30 min, respectively, NS), except for the aforementioned AHR-free patient (1.3 and 84.0 nM at baseline and 30 min, respectively), responsible for the divergence of the average pre- and post-DT exposure histamine levels. Yet, in all AHR-experiencing patients, following drug exposure to either DT or PT/pegylated doxorubicin, histamine levels remained within normal range, far below the anaphylaxis threshold (Table 4). Moreover, no relationship between AHR and pre- and post-DT exposure histamine levels has been documented (Table 5).

Serum tryptase remained within the normal range in all but two patients; yet there was no difference in levels before and after infusion (11.0 ± 35.0 and 11.3 ± 35.6 μg/l, respectively; NS) (Table 4). No correlation between tryptase levels and AHRs was found (14.1 ± 41.9 and 4.3 ± 2.6 μg/l in AHR-free and AHR-experiencing patients, respectively; NS) (Table 5). Notably, the two patients who were found to have increased serum levels of tryptase (above 200 μg/l), one receiving DT and one PT, did not experience any reactions to any course of chemotherapy.

Discussion

Few investigators have directly addressed and studied the nature of AHRs either to DT or to PT, despite the widespread use of both agents in cancer patients. The incidence of AHRs associated with DT varies among different studies. Burris *et al.* reported an 8.6% rate, but the overall incidence of AHRs in phase I studies was around 13%. Initial phase II studies without the use of pre-medication reported up to 31% of AHRs, but only 7% appeared to be severe [3,5]. An EORTC Early Clinical Trials Group reported a 26% AHR incidence with DT [4]. The great variation of AHR occurrence among these studies could be attributed to the diversity of symptoms

and signs associated with an AHR, and the inherent subjectivity of diagnosing and describing the events. Furthermore, different infusion schedules could affect AHR occurrence as shorter schedules tend to have increased AHR frequencies compared with more prolonged infusion schedules [2]. The various pre-medication regimens used may also contribute to this variation.

The frequency of DT-induced AHRs in this study (22.5%), although close to that of previous studies, is high despite the use of an intensive pre-medication schedule. Although the results of this study may be biased because of the small number of patients, they emphasize that both the true benefit and the best regimen of pre-medication remain unclear, as recently stated by other investigators reporting results of nine out of 415 taxane-treated patients in different studies [10].

The type and timing of reactions in this study were similar to those of other studies [1–5] with head/neck flushing and epigastric or back pain being the commonest findings, which always appear during the first 5 min of infusion. However, contrary to the 2% rate of severe hypotension, angioedema and bronchospasm previously reported (nine phase II studies [9]), no such reactions occurred in our patients and only one PT-receiving patient presented mild, rapidly subsiding bronchospasm. In the majority of AHRs arterial pressure and heart rate were maintained stable with only two cases of hypertension and tachycardia. Hypertension has been reported by at least one investigator [9]. Since none of these reactions could be considered as anaphylactic, all AHR-experiencing patients were carefully monitored without additional anti-allergic medications (e.g. epinephrine, hydrocortisone); as expected from the previously mentioned hypothesis as well as our experience, all reactions subsided *per se*, without any immediate or midterm complication.

Furthermore, all AHR patients were re-challenged 15–30 min after the initial reaction at a slower infusion rate and all but one patient successfully completed the treatment without reappearance of symptoms. However, the one patient who experienced a second reaction successfully completed the infusion with a third attempt at a slower rate, 30 min later.

As proposed by at least one study [9], these clinical observations are not consistent with an allergic origin of these reactions, since re-challenge should always reproduce the reaction. In our patients and in accordance with other investigators [2,10], DT-related AHRs tend to be infusion-rate related, a finding also inconsistent with an anaphylactoid reaction for which it is well known that even a minimal amount of an allergen may trigger sufficient mast cell mediator release to induce a severe reaction [11]. Conversely, other molecules, such as those with vasomotor activity, should reproduce the same reaction at each exposure, which argues against such a nature of AHRs.

Another feature of allergic drug reactions is that without previous exposure, a reaction occurs after several treatment days, since a period of initial sensitization is necessary after an uneventful initial therapeutic course. In our AHR patients, all reactions occurred during the first few drops or minutes of infusion. Since previous sensitization to the European Yew tree is unlikely, many previous studies have blamed the reactions on polysorbate 80, a component of the diluent, but which is at present found in many commonly used chemical substances. Even if this were true, each re-challenge with the same allergen should reproduce the reaction. However, all patients were given all the chemotherapy sessions without any evidence of acute or chronic allergy. An alternative explanation for the non reappearance of AHR after the 'immediate' re-challenge could be that, given the suppression of mast cells response from pre-medication, the anaphylaxis mediators were rapidly 'exhausted' after the first exposure to an allergen, allowing the 'safe' re-exposure, soon after. Nevertheless, the second or third and subsequent re-challenge after some days, when the mast mediators may have been restored, should reproduce the same phenomena, but eventually more severe. Yet, the same might be true in the case of release of other molecules such as vasoactive amines.

One might argue that the pre-medication used in our patients might have influenced the baseline and post-exposure levels of histamine and tryptase. Even if this is the case, in the presence of a histamine- or tryptase-induced AHR one would expect a rise of these mediators post-reaction, something that was not observed in our study.

Nannan Panday *et al.* [9] have put forth the hypothesis that DT reactions are non-immunological anaphylactoid reactions induced by mast cell histamine release, explaining the occurrence of reactions without prior sensitization. Again, the normal concentration of histamine during all AHRs in this study, as well as the lack of significant difference in this mediator between patients with and without AHRs, oppose this hypothesis and suggest that histamine cannot be implicated in the pathogenesis of this adverse effect. The fact that the only three patients with positive allergy markers (one with elevated histamine and two with elevated tryptase) did not experience AHRs corroborates the hypothesis of a non-allergic or at least a non-histamine/tryptase mediated allergy, further dissociating AHRs from classic drug-induced anaphylaxis [7,8].

The questionable reliability of histamine as a drug-allergy marker due to short and somewhat unpredictable presence in plasma might raise an objection; nonetheless, measurement at its proposed half-life and in comparison to baseline levels, as well as tryptase measurement, which is virtually absent from normal serum and has a longer serum half-life, make our results reliable [7,8].

Other biological processes that could be implicated in the mechanism of AHRs to DT are increased vascular permeability, release of anaphylatoxins and other chemotactic activators or the release of other vasoactive molecules such as serotonin, bradykinin and SRS-A [12]. Preliminary observations of an ongoing study in our department do not support the implication of serotonin or the complement cascade activation in DT-induced AHR.

Hypotheses for the mechanism of reactions to the other drugs of the study (PT and pegylated doxorubicin) cannot be made from this study, due to the small number of patients. However, not one PT- or pegylated doxorubicin-treated, AHR-experiencing patient had elevated histamine or tryptase. This finding together with the close clinical similarity of their AHRs to those of DT is strongly suggestive of a common pathogenesis.

Given the striking absence of positivity of the examined drug allergy markers, as well as the relatively small size of the sample, no subgroup analysis was possible. To our knowledge, this is the first study exploring the involvement of histamine and tryptase in the pathogenesis of DT-associated AHRs. If these results are confirmed by further studies, the role of co-medication drugs may be questioned. Glucocorticoids as co-medication with DT seem necessary at least for the prevention of fluid retention syndrome; however, the dose or schedule of administration could be modified in order to minimize short- and mid-to-long-term side effects. Yet, antihistamines (H_1 and H_2 antagonists) should be cautiously, if at all used, bearing in mind that some of them, in addition to their well known side-effects and interactions with other drugs, are potent inhibitors of cytochrome P450 system, thus potentially impairing elimination of DT, which is extensively metabolized by the P450 3A4 subfamily [12]. This might lead to unpredictably increased or modulated toxicity of DT.

The findings of the present study seem to be the 'proof of a principle' which suggests that AHRs to DT are neither histamine nor tryptase mediated and might not be anaphylactic or anaphylactoid in nature. Another pathogenetic mechanism should be explored, such as the release of vasoactive or other molecules.

In view of the above findings, the type of co-medication should be revised.

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