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Management of Infusion Reactions to Taxane Based Chemotherapy: Review Article

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ABSTRACT:
Background:
Virtually all chemotherapeutic agents have the potential to initiate infusion reactions, defined in this review as unexpected reactions that cannot be explained by the known toxicity profile of the drug. The cytotoxic agents that are most commonly associated with infusion reactions are the taxanes, platinum drugs, pegylated liposomal doxorubicin, L-asparaginase, procarbazine, etoposide, bleomycin, cytarabine, and ixabepilone. While these are often referred to as "hypersensitivity reactions," many do not have an allergic component. Thus, the term infusion reaction is preferred. When such a reaction occurs, clinicians can either continue the treatment, at the risk of causing a severe or a potentially fatal anaphylactic reaction, or stop the treatment. The objective of the present paper was to methods used to prevent and treat hypersensitivity reactions to taxane-based chemotherapy and to write evidence-based recommendations.
Source of data:
The scientific literature published to march 2016, was reviewed.
Conclusion:
Several strategies such as premedication, skin testing, and desensitization protocols are available to potentially allow for administration of taxane-based chemotherapy to patients who have had a infusion reaction and for whom no other treatment options are available. Considering the available evidence premedication significantly reduces the incidence of hypersensitivity to taxanes: skin testing does not appear to be useful for taxanes. A desensitization protocol allows for re-administration of taxane-based chemotherapy to some patients without causing severe hypersensitivity reaction.

KEYWORDS:- Infusion reactions, taxanes, desensitization, chemotherapy, management.

I. Introduction:

Taxanes are an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. Taxanes is classified as a "plant alkaloid," a "taxane" and an antimicrotubule agent. Taxanes is used for the treatment of breast, ovarian, lung, bladder, prostate, melanoma, esophageal, as well as other types of solid tumor cancers. It has also been used in Kaposi's sarcoma. Hypersensitivity symptoms generally develop within the first 10–15 minutes after infusion (78% within the first 10 minutes)1. In 95% of cases, reactions occur during the first or second infusion2, but reactions can appear during subsequent infusions (3%)1,2. Some patients also develop skin reactions several days or up to a week after infusion. The incidence of paclitaxel and docetaxel hypersensitivity varies between 8% and 50%. Diagnosis is facilitated by the clinical presentation and the time of appearance because the reactions are different for and specific to each agent.

DRUG	%	TIME OF ONSET	REACTIONS	SEVERITY
Paclitaxel	8–45	Within first minutes of infusion, during cycle 1 or 2	Dyspnea (with or without bronchospasm), urticaria, hypotension (or sometimes hypertension), erythema, back pain, chest pain, abdominal l or pelvic pain	Minor reactions 40% of patients Severe reactions 1.3% of patients
Docetaxel	25–50	Within first minutes of infusion, during cycle 1 or 2	Dyspnea (with or without bronchospasm), urticaria, hypotension (or sometimes hypertension), erythema, fluid retention syndrome	Severe anaphylactic reactions in 2% of patients

Risk Factors

In the case of paclitaxel, hypersensitivity reactions occur more often in patients with a history of atopy3. For both docetaxel and paclitaxel, a history of mild skin reactions during earlier treatments; the presence of respiratory dysfunction, overweight, or obesity; and menopausal or postmenopausal status have also been

reported as risk factors4-6. Whether hypersensitivity can be attributed to the taxanes themselves or to their formulation vehicles has not yet been established 7–8. Paclitaxel is administered in a solution of ethanol and Kolliphor el (formerly Cremophor el: BASF, Ludwigshafen, Germany), which is also used as a vehicle for other compounds known potentially to cause hypersensitivity (cyclosporine, teniposide, diazepam, propofol, and vitamin K)9. However, studies have shown that Kolliphor used without paclitaxel and without premedication does not trigger hypersensitivity reactions10. The reaction to docetaxel has been attributed to its vehicle, polysorbate 80, which is also used for etoposide29. However, data have shown that the drug itself might be the cause of hypersensitivity11.

Infusion Time and Premedication Infusion

A meta-analysis evaluated the impact of paclitaxel infusion time and showed no difference in the risk of developing hypersensitivity when treatment was administered over 3 or 24 hours (risk ratio: 1.86; 95% confidence interval: 0.63 to 5.52)12. Furthermore, Hainsworth et al.13 noted no difference in activity between 1-day and 3-day paclitaxel schedules in which each dose was administered by 1-hour infusion.

Routine premedication with glucocorticoids can diminish the incidence of hypersensitivity during paclitaxel or docetaxel therapy from 30% to 3%14. With premedication, the incidence of hypersensitivity reactions to paclitaxel is between 1% and 3% regardless of infusion time (1, 3, or 24 hours). Kwon et al.49 showed that, compared with a single administration 30 minutes before treatment, administration of dexamethasone 12 and 6 hours before infusion of paclitaxel led to fewer hypersensitivity reactions; another study showed no difference15. Premedication with dexamethasone (8 mg for 3 days starting the day before infusion) can reduce the incidence of grade 3 or 4 hypersensitivity reactions to docetaxel to about 2%16,17. As a result, the median cumulative dose administered before the incidence of severe symptoms increased (from 490 mg/m2 to 790 mg/ m2) 18. Chouhan et al.19 showed that a single dose of dexamethasone 30 minutes before docetaxel infusion was sufficient to prevent hypersensitivity reactions.

II. Treatment of Hypersensitivity Symptoms:

Early recognition of hypersensitivity reactions is essential for the patient's well-being and can, in some cases, save lives. Patients must be informed of adverse events so that they can contact medical personnel as soon as possible. Treatment must be interrupted immediately when a patient develops a hypersensitivity reaction. Depending on the symptoms, it might be necessary to administer medication. Antihistamines, corticosteroids, and if necessary, epinephrine and bronchodilators should be administered, and oxygen should be readily available. In the case of a severe reaction, treatment should not be continued. However, with a mild reaction, treatment can be resumed the same day20-21. In many cases, a mild-to-moderate reaction will resolve after a brief interruption of treatment and administration of appropriate medication22. Re-treatment has the potential to have serious consequences, and close monitoring is therefore essential during the next cycle

III. Substitution of Therapy:

A new formulation of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) avoids the use of Kolliphor as a vehicle, and thus premedication is not required23. No hypersensitivity reactions were reported in several phase i, ii, and iii studies that used this agent24, and administration of nab-paclitaxel was well tolerated in 5 patients who had previously experienced hypersensitivity reactions to paclitaxel25. However, one phase iii study indicated that nab-paclitaxel can cause hypersensitivity reactions26.

IV. Desensitization Protocols:

Desensitization is indicated when no alternative therapy exists or when the available alternative is less effective than the treatment being used. Desensitization protocols involve inducing a temporary tolerance to a treatment by gradually reintroducing a small amount of the antigen over a relatively short period of time until the total scheduled dose has been administere27. Because a desensitization protocol induces only a temporary tolerance, it must be carried out every time the patient receives the treatment 28. A 12-step desensitization protocol has been developed by the Dana–Farber Cancer Institute and the Brigham and Women's Hospital29,30. Unlike most of the other protocols, it is the only one to have been successfully used during several hundred desensitizations for multiple antineoplastic agents. The protocol involves the preparation of three different solutions with escalating concentrations of the drug (Table iI). The infusion rate changes every 15 minutes, and the volume infused is approximately double that of the preceding step. As reported in three publications, use of this 12-step protocol resulted either in no hypersensitivity reaction or in a less-severe reaction than the reaction that originally led to the need for desensitization.

In 2005, Feldweg et al.29 reported the results of paclitaxel and docetaxel desensitization for patients admitted to a desensitization protocol because of severe hypersensitivity reactions (dyspnea, laryngeal edema,

bronchospasm, oxygen desaturation, chest pain, significant change in blood pressure, or loss of consciousness) during prior treatment. During desensitization, 4 patients developed a reaction. The reactions were less severe than the original ones (palmar–plantar erythema, abdominal pain, burning sensation in the chest, and moderate flushing). Treatment was interrupted, and the patients received diphenhydramine. One patient had complications warranting readmission to hospital. That patient opted for a change in treatment; the other three underwent subsequent desensitizations using the standard or a modified protocol without any reactions.

In 2008 and 2010, Castells et al.30 and Limsuwan and Castells published the results of desensitizations for carboplatin, paclitaxel, cisplatin, oxaliplatin, and other treatments (rituximab, liposomal doxorubicin, and doxorubicin). To be eligible, patients had to have experienced a hypersensitivity reaction during or within 48 hours after infusion. Of all the desensitizations, 94% produced a mild reaction or no reaction. All reactions were controlled by interrupting treatment and administering appropriate medication, with epinephrine needed for 1 patient. Overall, 7% of reactions occurred during steps 1–4, 18% during steps 5–8, and 75% during steps 9–12, with 51% of reactions occurring during the last step of the desensitization protocol. All patients received their treatment at full dose. Other multi-step desensitization protocols of 4–13 steps have been suggested31. Most patients completed them with few or no hypersensitivity symptoms. Other multi-step desensitization protocols of 4–13 steps have been suggested32. Most patients completed them with few or no hypersensitivity symptoms.
General principles of the 12-step desensitization protocol

Step	*Solution*	*Rate (mL/h)*	*Time (minutes)*	*Volume infused per step (mL)*
1	1:100 dilution of the final target concentration	2	15	0.5
2		5	15	1.25
3		10	15	2.5
4		20	15	5
5	1:10 dilution of the final target concentration	5	15	1.25
6		10	15	2.5
7		20	15	5
8		40	15	10
9	Usual concentration; cumulative dose administered in steps 1–8	10	15	2.5
10		20	15	5
11		40	15	10
12		75	Prolonged until complete dose	232.5

V. Discussion

Hypersensitivity /Infusion reactions to chemotherapy are unpredictable adverse events with potentially lethal consequences. Among the agents most likely to cause this type of reaction are taxanes. Literature on this subject often comes from case studies and populations consisting of a limited number of patients. Further research is needed to validate the reported information.

using premedication with taxanes can diminish the risk of hypersensitivity reactions, Modifying the infusion time seems to have an effect on the risk of having a reaction to some agents, but additional research is needed to clarify this issue. The desensitization protocols for platinum drugs and taxanes discussed earlier in this article were administered to 15 or more patients and are based on administering treatment in numerous dilutions and gradual steps. The associated success rate is nearly 100%, with no severe hypersensitivity reactions in most cases. The large-scale studies reported by the Dana–Farber Cancer Institute and Brigham and Women's Hospital describe a 12-step protocol tested on a larger group of patients undergoing a significant number of desensitizations involving platinum drugs and taxanes33. In every case, the planned therapy was successfully administered, with no hypersensitivity reactions or with just mild reactions, all of which were less severe than the initial ones. Premedication was administered before desensitization for taxanes. When hypersensitivity reactions occurred during the desensitization protocol, administration of antihistamines and interruption of treatment successfully controlled the symptoms in most cases and allowed the protocol to be completed. During subsequent desensitizations, a modified protocol allowed for all patients to receive the scheduled number of treatment cycles.

All personnel involved must be trained to recognize hypersensitivity reactions and to respond immediately. Emergency medications— including epinephrine, antihistamines, bronchodilators, and oxygen— must be at the patient's bedside to ensure quick administration if needed. Patients must be educated to recognize early symptoms and to immediately inform the medical staff.

VI. Conclusions And Recommendations

With respect to taxanes (paclitaxel, docetaxel): Premedication with glucocorticoids and H1 and H2 antagonists should routinely be administered to reduce the risk of hypersensitivity reactions (grade A recommendation). Skin testing is not recommended for identifying hypersensitivity reactions to taxanes (grade B recommendation).

With respect to desensitization: A multi-step desensitization protocol can be used in the case of a positive skin test for platinum drugs or a type i hypersensitivity reaction if treatment cannot be substituted and if stopping treatment would affect the patient's survival (gradeB recommendation). The 12-step protocol developed by Castells et al. 41 is supported by the best evidence. The desensitization protocol must be carried out under appropriate supervision and closely monitored, with all necessary equipment at hand (grade D recommendation): Medical personnel in attendance must have been trained to recognize hypersensitivity reactions and must be prepared to respond immediately. ◦ Emergency medications (epinephrine, H1 and H2 antihistamines, bronchodilators, and oxygen) must be at the patient's bedside to ensure quick administration as needed. Patients should be educated to recognize the initial symptoms of hypersensitivity and to immediately inform attending personnel (grade D recommendation). Premedication must be administered before any desensitization protocol (grade D recommendation). If a hypersensitivity reaction should occur during the protocol (grade D recommendation), then the infusion must be interrupted and the symptoms controlled by appropriate medication. , the protocol must be adjusted such that the full dose can be administered if possible. , the protocol must be modified for subsequent desensitizations. , a desensitization protocol must be conducted every time the patient subsequently receives treatment.

CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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