Taxane therapy associated adverse ocular reactions

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Abstract

The adverse ocular reactions to paclitaxels involve a series of damage, which can be observed on ocular surface, ocular appendages and intraocular tissues. They can appear as various clinical symptoms including dry eye, lacrimal duct obstruction, conjunctivitis, keratitis, macular edema, retinal injury, optic nerve injury, and etc. All these symptoms may lead to irreversible visual loss. The mechanisms of these side effects are still unclear. Macular edema, one of the side effects, may be related to the dysfunction of retinal pigment epithelial (RPE) cells and Müller cells which is caused by paclitaxel, while other symptoms may be caused by the cytotoxicity of paclitaxels. In this review, we describe the widely accepted drug-induced ocular disorders and the possible mechanisms, so as to provide some suggestions for the monitoring and management of ocular toxicity.

Taxane Therapy Associated Adverse Ocular Reactions

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【**Abstract**】 The adverse ocular reactions to paclitaxels involve a series of damage, which can be observed on ocular surface, ocular appendages and intraocular tissues. They can appear as various clinical symptoms including dry eye, lacrimal duct obstruction, conjunctivitis, keratitis, macular edema, retinal injury, optic nerve injury, and etc. All these symptoms may lead to irreversible visual loss. The mechanisms of these side effects are still unclear. Macular edema, one of the side effects, may be related to the dysfunction of retinal pigment epithelial (RPE) cells and Müller cells which is caused by paclitaxel, while other symptoms may

be caused by the cytotoxicity of paclitaxels. In this review, we describe the widely accepted drug-induced ocular disorders and the possible mechanisms, so as to provide some suggestions for the monitoring and management of ocular toxicity.

【**Key words**】 Paclitaxel, Eye diseases, Drug related side effects and adverse reactions

As the first natural phytochemical drug approved by Food and Drug Administration (FDA), Paclitaxel (Taxol) is an anti-tumor drug with highly efficacy and low toxicity. As taxane widely served as an anti-tumor drug, the number of reports on its adverse side effects is climbing rapidly, mainly including bone marrow suppression, allergic reaction, digestive system reaction, numbness of the hand and foot, liver injury, and etc. However, in recent years, there have been reports of adverse ocular reactions caused by taxane drugs. Such as vision loss [1], dry eye [2], lacrimal duct obstruction [3], conjunctivitis [4], glaucoma [5], optic neuropathy [6], macular edema [7, 8], blindness caused by combination with cisplatin [9], and so on. These adverse side effects have numerous effects on patients' life quality and their compliance to the therapy. In order to have a comprehensive understanding of the ocular adverse sides caused by taxane drugs as well as and their possible mechanisms in side effects and to improve the safety of the administration, we briefly reviewed the relevant literatures at home and abroad.

1 Taxane

Taxol (general name paclitaxel) is the first microtubule-stabilizing drug of taxane family isolated from the yew root. In 1967, Mansukh Wani and Monroe Wall had isolated and identified the active ingredient from the bark of *T. brevifolia* and named it taxol, basing on its species of origin and the presence of hydroxyl groups [10]. Taxol enters phase I clinical trials in 1894 and phase II clinical trials in 1895. In the United States, the Phase III clinical trial was completed in 7 years from 1983 and was approved by the FDA in 1992[11]. Taxol has been obtained by chemical semi-synthesis, total chemical synthesis, tissue and cell culture, microbial fermentation and biosynthesis. In 1995, docetaxel, the second member of the family was approved for medical use. Due to the poor water-solubility of paclitaxel before, solvent-increasing polyoxyethylene castor oil and anhydrous ethanol will be added when it is used [12]. As the solvent itself will cause severe allergic reactions, there were various limitations to clinical use.

Advances requires to be made because of various restrictions mentioned above. Currently, paclitaxel family includes traditional paclitaxel, paclitaxel liposome, paclitaxel nanoparticle albumin bound (NAB)(Abraxane) and docetaxel (Taxotere). Unlike other microtubule-stabilizing anticancer drugs which prevent the assembly of tubulin into microtubules, it is a microtubule stabilizer (anticontractile agent) and a mitotic inhibitor (antiproliferative agent) [10]. Paclitaxel promotes the assembly of tubulin to microtubules and prevents the dissociation of microtubules as well as blocks cell cycle progression, prevents mitosis, and inhibits the growth of cancer cells [11]. Thus, paclitaxel has become a widely accepted chemotherapeutic drug in the treatment of ovarian cancer, breast cancer, non-small cell lung cancer and a variety of other malignant solid tumors [13].

2 Occurrence of adverse ocular side effects

The adverse ocular sides effects of taxane drugs involve ocular appendage and various intraocular tissue structures, with various clinical manifestations but no specificity. Eye diseases caused by taxane mainly include dry eye, conjunctivitis, glaucoma, retinopathy and optic neuropathy. According to the Drug Instructions, the injectable paclitaxel (albumin-bound) specification states that eye/visual adverse events occurred in 13% population (48/366) of clinical studies in the United States and Europe, while severe cases occurring in 1% population. The main symptoms were keratitis and blurred vision which were usually reversible. In a phase I clinical study of Chinese patients, 1 out of 104 patients developed transient blurred vision and diplopia. In a randomly controlled clinical study of Chinese patients with metastatic breast cancer, 4 out of 100 patients developed mild blurred vision, which was transient and self-healing. Noguchi [14] has conducted a retrospective study of risk factors concerning ocular disorders caused by paclitaxel and NAB-paclitaxel. This retrospective study targeted patients who were newly treated with paclitaxel or NAB-paclitaxel at Kyoto Okamoto Memorial Hospital between April 1, 2012, and March 31, 2017. Of 128 subjects, 13 (10.2%)

had ocular disorders with symptom ranging from grades 1 and 2. The symptoms included conjunctivitis or subconjunctival hemorrhage (3.1%), visual acuity reduction (2.3%), blurred vision and eye pain (1.6% each), eye mucus, blepharitis, stye, watering eyes, photopsia, and muscae volitantes (0.8% each). Alvarez–Fernandez et al. [15] shared a 73-year-old patient with metastatic breast cancer who developed macular edema after being treated with paclitaxel, which disappeared after drug withdrawal. In this paper, 57 cases of paclitaxel-related macular edema reported in 52 literatures were analyzed. The median time of occurrence of macular edema after taking the drug among these patients was 4.25 months. Among these patients, 92.86% were diagnosed as macular edema and bilateral vision loss in the initial examination, and most of their symptoms reversed after paclitaxel withdrawal.

3 Clinical manifestations and possible mechanisms of adverse ocular sides effects

3.1 Involvement of ocular surface and appendages

The most common symptoms are discomfort of the eyelids, conjunctiva and lacrimal gland organs, including dry eye [2], nasolacrimal duct obstruction [16], lacrimal duct obstruction [16-18], erosive conjunctivitis and punctate stenosis [4], corneal epithelial lesions [19, 20], and limbal stem cell deficiency [3]. The obstruction of nasolacrimal duct may be related to the interstitial fibrosis of lacrimal duct mucosa [16]. And conjunctiva, keratopathy and dry eye may be related to the cytotoxicity of the drug. The drug inhibits cell proliferation in the cornea and eye surface, leading to stem cell dysfunction, and then triggers inflammation of the conjunctiva and epithelial defects [19]. However, the mechanisms of the injury of ocular surface and accessory organ is still needed to be investigated.

3.2 Intraocular tissue damage

Intraocular tissue (lens and vitreous) damage caused by taxane is rare. Kuwata et al. [21] evaluated the ocular toxicity of different doses of paclitaxel to Sprague-Dawley (SD) rats of different ages. The results showed that the dose of 4 or 8 mg/kg of PTX injected into 0-day-old rats resulted in epithelial cells of the lens apoptotic, and the lens fibers were degenerative on the 7th day. These phenomena suggested the occurrence of cataract. However, no ocular lesions were observed at the dose of 2 mg/kg of PTX injected into 0-day-old rats. At the same time, no ocular lesions were observed in rats injected intraperitoneally with 4 mg/kg paclitaxel at 14 days of age and 8 mg/kg paclitaxel at 12 to 18 weeks of age. These results suggested that the ocular toxicity of paclitaxel may be dose-related and age-related, and attention should be paid to the ocular toxicity of paclitaxel in early developmental stage. But the mechanisms are still under water.

3.3 Retinal injury

The incidence of retinal injury is rare, which appears mainly as macular edema. The primal symptom of macular edema caused by taxane is impaired vision acuity. Kaya et al. [7] reported 202 patients who received taxane-based therapy due to treatment of various cancer, taxane-related cystoid macular edema (CME) was detected only in one patient on paclitaxel. Generally, the proportion of taxane-related maculopathy was 0.5% (1/202) of all patients in the taxane group. However, this particular macular edema, which has the characteristics of not presenting the classic angiographic findings link to other macular edema (eg, diabetic macular edema (DME), macular edema secondary to retinal vein occlusion (RVO-ME) or uveitis) in a straightforward manner. In the macular edema caused by tanxane, optical coherence tomography (OCT) showed increased thickness of macular fovea, and fundus fluorescence angiography (FFA) examination did not reveal any source of leakage. In addition, macular edema will disappear spontaneously after drug withdrawal. The pathological mechanisms for this particular type of macular edema are still unclear of which there have no histopathological studies but only case reports yet. However, there are different speculations about the pathogenesis of taxane-induced macular edema. On the one hand, some scholars believe that such drug-induced macular edema may be caused by cytotoxicity caused by paclitaxel which inhibits intracellular microtubule recombination [22]. On the other hand, others, such as Nomi, consider that the mechanisms could be internal accumulation of intracellular fluid and minimal impairment of the blood retinal barrier (BRB) [8]. Another theory, which would also explain the angiographic findings, would be that the edema was due to an accumulation of fluid in the intracellular space. At the same time, other scholars interpreted

the imaging results of no leakage or minimal leakage as Müller cells cytotoxicity. Because Müller cells are responsible for maintaining the nerve sensory osmotic gradient in the retina, and their dysfunction leads to the accumulation of intracellular fluid [1]. Besides, it has also been found that the electroretinogram (EGR) b wave parameters are normal and the Arden ratio is low, suggesting RPE involvement [23].

Meanwhile, through experiments on animals, Kuwata et al [21] found that ocular toxicity of different doses of paclitaxel to newborn SD rats of different ages also showed that retinal dysplasia occurred after intraperitoneal injection of 4 or 8 mg/kg paclitaxel in 0-day-old SD rats. This suggested that the ocular side effects of paclitaxel were related to the duration and concentration of the drug. In our current study, we found in vivo that the same mice were injected with the drug for different time, and the visual electrophysiological examination showed that the time of receiving the drug was longer and the eye damage was more serious. In vitro experiments, we detected the survival ability of RPE cells and Müller cells, and found that the survival ability of cells receiving the same concentration of drug stimulation for a longer time was worse. Those who received higher doses of the drug for the same time had poorer cell survival. (unpublished data).

3.4 Optic nerve injury

Hofstra et al. [24] mentioned a case of ovarian cancer patients received 6 times of paclitaxel intraperitoneal chemotherapy after sudden blindness, does not appear to have a headache, nausea, or other central nervous system symptoms. Eye examination showed his eyes left hemianopsia, prompt visual cortex damage. Ease withdrawal symptoms after 10 d, diagnosis of vasospasm caused by optic nerve function defect. It may be related to intraperitoneal chemotherapy with paclitaxel. When paclitaxel was infused, patient experienced scotomata small luminous dotsor "flies" in the visual fields of both eyes, lasted a few minutes to several hours. It was speculated that paclitaxel may damage the optic nerve [25]. Sediman et al. [6, 23] estimated that among 25 breast cancer patients who received paclitaxel 250-275 mg/m^2 chemotherapy for the first time, 6 of them saw the flashing of stars or fireworks in the whole field of vision 3 h after the chemotherapy which usually last 15 min to 3 h. There were no significant chronic sequelae. And this phenomenon occurred again when the same or slightly lower dose of chemotherapy (less than 275 mg/m^2 but not less than 250 mg/m^2) was received, but wouldn't appear when the dose was less than 250 mg/m^2. It was considered to be a transient optic nerve vasogenic reaction induced by paclitaxel, dose-dependent and reversible. In addition, docetaxel treatment resulted in visual loss, intraocular pressure, enlargement of the optic cup, and loss of bilateral visual field [5, 26]. There are studies that evaluated visual electrophysiology in 14 breast cancer patients undergoing paclitaxel chemotherapy. ERG b-wave latency significantly increased. Seven patients showed abnormal ERG, oscillating potentials, 30 Hz flashing light response and visual evoked potentials (VEP) monitoring in different combinations, twelve patients presented with transient dark spots and blurred vision with abnormal oscillating potentials. It suggested that the most likely mechanism of visual symptoms and electrophysiological changes during paclitaxel administration is vascular dysregulation in the retina, or ischemic mechanisms when the optic nerve is involved [27]. In a study of 47 patients who received paclitaxel for non-small lung cancer, three of them showed abnormal VEP, showing a significant decrease in P100 amplitude and a slight increase in latency. The abnormal increase in P100 latency of VEP is considered to be typical demyelinating optic neuropathy [28].

4 Prevention and treatment

For patients under taxane administration, it is recommended to have a baseline examination of ophthalmology before treatment, such as visual acuity, intraocular pressure, fundus, color vision, visual field examination, and etc. and to closely observe whether there are new ocular symptoms during the treatment process. Patients with ocular symptoms in the course of medication should be referred to have ocular consultancy and have a complete ocular checkup in time. For the ocular surface diseases caused by paclitaxel drugs, such as dry eye, conjunctivitis, keratitis, and etc. Usually, we recommend to use artificial tears, non-steroidal anti-inflammatory drugs, antibiotic eye ointment and other symptomatic treatment. Lacrimal duct obstruction or narrow, tear overflow can be used lacrimal duct irrigation or lacrimal duct exploration [19]. The adverse side effects occur on the ocular surface caused by paclitaxel are reversible and can be recovered after withdrawal and symptomatic treatment, with within several days to 5 months [19].

For patients with macular edema and impaired vision, there are no authentic treatment guidelines. The main treatment strategy is to stop chemotherapy, but this option should be mainly determined by the systemic status. Some scholars have tried to use carbonic anhydrase inhibitors, glucocorticoids and anti-vascular endothelial growth factor drugs for treatment. Ehlers et al. [29] showed that topical use of 2% carbonic anhydrase inhibitors could effectively remission paclitaxel-associated macular edema and improve visual acuity after the cessation of chemotherapy, suggesting that carbonic anhydrase inhibitors might be used as an early treatment option. Glucocorticoids are also being considered. In cases that dexamethasone was injected intravitreally, the retinal thickness of the patient decreased after 1 month, but the macular edema persisted and the presence of macular edema disappeared significantly after 2 months of discontinuation of chemotherapy [30]. The similar finding was also observed in cases subjected to sub-Tenon injections of triamcinolone acetonide, suggesting that glucocorticoids may merely relieve rather than resolve the problem [31]. Anti-vascular endothelial growth factor drugs, a widely adopted drug in treating diabetic macular edema, seemed has little effect to paclitaxel-induced macular edema. In Rahman's study, continuous binocular intravitreal bevacizumab resulted in stable vision but persistent macular edema [32], which reveals the different mechanisms of taxanes induced macular edema from diabetic macular edema and retinal vein occlusion-macular edema. In addition, some researchers have found that carvone protects against paclitaxel-induced retinal and optic nerve cytotoxicity in rats[33], while further studies remain to be carried out.

5 Conclusion

The adverse ocular side effects of taxane drugs mainly appear on the ocular surface, ocular appendage and intraocular tissue structure, with various clinical manifestations such as dry eye, conjunctivitis, keratitis, macular edema, retinal injury, optic nerve injury, and etc. The hidden mechanisms remain elusive. The macular edema induced by taxane drugs may be related to the dysfunction of retinal pigment epithelial cells and Müller cells, and other adverse reactions may be related to the cytotoxicity of paclitaxel. Before the application of paclitaxel drugs, baseline examination of ophthalmology is necessary. Ocular symptoms should be closely observed during the administration. Eye adverse reactions can be clearly diagnosed through routine ophthalmic examination. Once found, chemotherapy should be considered to be adjusted according to comprehensive evaluation, and symptomatic treatment can be given, so as to avoid irreversible eye injuries.

Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Authors' Contributions

Ya-Ting Ye and Zi-Yi Zhou wrote the manuscript. Li-Shi Wen, and Yu Sun participate to assist this work. Guo-Rui Dou and Zhao-Jie Chu reviewed the manuscript. Guo-Rui Dou provided thoughtful comments and suggestions during this review preparation. All authors read and approved the final manuscript.

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