Review article

Ocular side effects of the taxane-based chemotherapy – do only vascular disorders matter?

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ABSTRACT

Taxanes, whose mechanism of action is based on blocking the cells' division of cells, have been commonly used in the chemotherapy process for over two decades. The indications for the use of taxanes include ovarian cancer, breast cancer, lung cancer, prostate cancer, some of gastrointestinal malignant tumors or Kaposi sarcoma. Currently, chemotherapy based on taxanes, as well as every cytostatic medicine, allows to improve survival outcomes in many patients with diagnosed malignancies, although it also involves the occurrence of adverse effects. These adverse events may be life-threatening or at least they can decline the patient's quality of life. The main aim of this paper is to feature possible ocular side effects during taxane based chemotherapy. Physicians taking care of patients during chemotherapy based on taxanes, as well as on every other cytostatic medicine, should be aware of these probable ocular complications. An early diagnosis of ophthalmic complications caused by chemotherapy makes it possible to avoid long-lasting adverse effects.

Key words: taxanes, chemotherapy, ophthalmological complications

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INTRODUCTION

Taxanes as cytotoxic drugs have been commonly used in chemotherapy for over 20 years. Taxanes' mechanism of action is based on the inhibition of mitotic spindle. They bind to the microtubules' beta-tubulin subunits (which in normal conditions are highly dynamic intracellular structures and change their length using energy from GTP), inhibit depolymerization [1] and prevent cells division [2, 3].

Paclitaxel was the first taxane derived from bark of yew – *Taxus brevifolia* in 1962. Scientists confirmed its anti-cancer activity, however, it took years before they managed to describe paclitaxel's chemical structure and specify mechanism of action. Also, the threat of the yew extinction significantly extended the period of clinical trials. Eventually, paclitaxel was approved for use in cancer chemotherapy in 1993 [4, 5]. Today the drug is obtained using genetic engineering methods. Paclitaxel is used in chemotherapy of ovarian cancer, breast cancer, advanced non-small cell lung cancer and Kaposi's sarcoma [6].

In 1986 another taxane – docetaxel was synthesized. It was obtained from non-cytotoxic precursor – other yew species called *Taxus baccata*. Docetaxel was approved for the medical use 9 years later in 1995 [7]. The drug is used for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, head and neck cancer, stomach cancer [8].

Currently, other types of taxanes such as nab-paclitaxel (albumin-bound paclitaxel) and cabazitaxel are used in different chemotherapeutic regimens. Indications for the use of nab-paclitaxel include metastatic breast cancer in patients, who have failed first-line therapy and who may not receive standard anthracycline therapy. Moreover, nab-paclitaxel in combination with gemcitabine is also used in the metastatic pancreatic adenocarcinoma treatment, while in combination with carboplatin as the first-line treatment of non-small cell lung cancer in adult patients who are not eligible for surgery and/or radiotherapy [9]. The newest taxane registered in 2010 – cabazitaxel is used in chemotherapy of hormone-refractory prostate cancer as a second-line treatment if docetaxel chemotherapy fails [10].

Myelosuppression (mainly neutropenia), peripheral sensory neuropathy, muscle pain, arthralgia and alopecia are the most common systemic side effects of taxanes [11, 12]. Cardiovascular complications include fluid retention (especially during docetaxel therapy), arrhythmias or heart failure [13]. Ophthalmologic side effects of taxane-based chemotherapy are much less common or are not reported as frequently as they should. They include the cystoid macular edema, toxic optic neuropathy, photopsies, glistening scotoma, excessive tearing. It is presumed that some of the ophthalmologic adverse effects during taxane chemotherapy may be caused by vascular disorders of the retina or the optic nerve.

OPTIC NEUROPATHY

Many case reports describe visual disturbances including flashes, decreased visual acuity or visual field defects in patients with diagnosed breast or ovarian cancer treated with paclitaxel. Patients usually reported these symptoms at the end of the infusion of the drug. In the majority of the cases, these symptoms resolved within a few hours after the end of the drug administration, but in some of the patients symptoms were persistent despite the discontinuation of the paclitaxel-based chemotherapy [14, 15]. Patients' subjective ocular symptoms were confirmed in electrophysiological studies, which showed changes within the retina and in the visual pathway [16].

Also, docetaxel chemotherapy is one of the risk factors of the optic neuropathy. One of the case reports describes the patient after docetaxel chemotherapy presented decreased visual acuity, colour vision deficiency, visual field defects. An ophthalmological examination revealed bilateral optic disc edema and hemorrhage within the disc. Other possible causes of visual impairment were excluded. After discontinuation of docetaxel chemotherapy and glucocorticosteroids implementation, symptoms gradually subsided [17].

Cabazitaxel, that is used for prostate cancer treatment may also cause ocular side effects such as decreased visual acuity, impaired color vision or visual field defects secondary to optic neuropathy [18].

The pathomechanism of how taxanes cause neuronal changes in the retina and the optic nerve is still unknown, but there are several theories. Some researchers assume that the cause of ocular symptoms and changes in electrophysiological tests during taxane therapy is a vascular disorder and vasoconstriction within the retina and the optic nerve, while others suspect that the optic nerve dysfunction is secondary to their neurotoxicity [16, 17]. The risk of neurotoxicity may also increase by using treatment regimens based on taxanes and platinum-based agents that have a similar toxic effect on the nervous system [19].

CYSTOID MACULAR EDEMA (CME)

Cystoid Macular Edema (CME) is defined as a thickening of the retina in the macular region. Blood-retinal barrier breakdown

leads to the peri-retinal capillaries leakage and the accumulation of the fluid within the retinal layers [20]. Symptoms of the cystoid macular edema include: decreased visual acuity, distorted vision (metamorphopsia), decreased contrast sensitivity, central scotoma in the visual field. The most common causes of cystoid macular edema are diabetes, age-related macular degeneration (AMD), Irvine-Gass syndrome, uveitis, central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) and the use of drugs such as thiazolidinediones, tamoxifen, topical ophthalmic drugs – epinephrine, E2-prostaglandins, timolol. The typical finding if the CME is caused by the above mentioned factors is the presence of retinal fluid leakage in fluorescein angiography. Cystoid macular edema without the capillary leakage from retinal vessels is not observed that often and it can be caused by juvenile retinoschisis, Goldmann-Favre syndrome, some types of retinitis pigmentosa, phototoxicity, drugs such as niacin (used to treat patients with hypercholesterolemia) [21] or drugs, which affect microtubules like taxanes.

Cystoid macular edema secondary to taxane chemotherapy (especially secondary to paclitaxel) is usually bilateral. The absence of contrast leakage in fluorescein angiography and a spontaneous visual acuity improvement is often seen after discontinuation of taxane therapy [22].

The main cause of the cystoid macular edema during taxane-based chemotherapy is still unknown. Some scientists assume that it is the result of Müller cell dysfunction. Cells dysfunction caused by taxanes involving the inhibition of microtubule polymerization and intracellular transport within Müller cells probably leads to accumulation of intracellular fluid [23, 24]. Another possible cause of the cystoid macular edema during taxane-based chemotherapy is the dysfunction of retinal pigment epithelial cells – precisely the dysfunction of microtubule-dependent intracellular transport from the top to the base of retinal pigment epithelium (RPE) cells [25]. As a consequence, impaired RPE cells are unable to pump out the fluid. The fluid accumulates within the retina, which leads to CME. It is also presumed that cystoid macular edema due to taxane chemotherapy is an effect of subclinical leakage from the retinal vessels. Probably only the substances smaller than fluorescein can penetrate through the blood-retinal barrier [25]. Therefore, there will be no signs of fluorescein leakage. Also, the fluid retention, which is often described after docetaxel chemotherapy, can cause the fluid accumulation within retina and the CME symptoms [26].

It is still unknown, why only some of the patients develop CME after taxane-based chemotherapy. Chelal et al. [27] examined 25 patients treated with taxanes for breast cancer, esophageal cancer and ovarian cancer. They found an increased macular thickness in the optical coherence tomography (OCT) scans with no evidence of cystoid macular edema in all of the patients. None of the patients had ophthalmological symptoms. Most of them were women (88%) with diagnosed breast cancer and treated with docetaxel (92%).

Further research are required to explain the pathomechanism of cystoid macular edema after taxane-based chemotherapy. Although, in most of the described cases the symptoms of cystoid macular edema receded after discontinuation of taxane therapy, nevertheless, in some patients, visual disturbances were persistent [28].

OTHER OCULAR COMPLICATIONS DURING TAXANE CHEMOTHERAPY

Excessive tearing (epiphora) is a relatively common complication after docetaxel-based adjuvant chemotherapy. Even 80% of patients, who received docetaxel chemotherapy, had problems with excessive tearing [29, 30]. Esmaeli et al. [31] proved that docetaxel is excreted into tears after intravenous administration. Some authors assume that tear duct obstruction may be caused by the presence of chronic inflammation and subsequent fibrosis within the tear duct stroma [32]. However, Chan et al. [30] observed the presence of epiphora in both group of patients – those with lacrimal punctum or lacrimal canal obstruction and those with maintained tear duct patency. Probably there are several pathomechanisms that cause excessive tearing after docetaxel treatment. Long-term therapy, as well as high cumulative doses of the drug are associated with a greater risk of epiphora. Patients, who received docetaxel in the weekly schedules required ocular surgical treatment due to excessive tearing more often than those patients, who received the same drug every 3 weeks [29]. In some patients, epiphora resolved spontaneously a few months after completion of chemotherapy with docetaxel. However, irreversible structural changes in the tear ducts are also possible. Excessive tearing can significantly reduce patients quality of life. Therefore, it is extremely important to detect possible changes in the tear ducts and treat them as soon as possible. Patients with symptoms of epiphora should be carefully examined. An assessment of the anterior segment, lacrimal puncta, lacrimal duct, as well as Schirmer test and lacrimal system probing must be conducted. Topical steroids, probing and irrigation of the tear duct may improve the clinical condition even after a short-term therapy. Because of a greater risk of stenosis, early intubation of the tear ducts may be considered in patients receiving docetaxel in weekly doses. When a tear duct obstruction occurs invasive surgical treatment like dacryocystorhinostomy (DCR)

(creating a fistula between the nasal sac and the nasal cavity) seems to be the best therapeutic option [33, 34].

Other ophthalmic adverse effects of taxane-based chemotherapy include eye pain, conjunctivitis or entropion after docetaxel treatment [35].

GENERAL DISEASES OR DRUGS SIDE EFFECTS?

Chemotherapy ocular side effects, including these caused by taxanes, are rare or rather rarely reported. Patients receiving oncological treatment are usually older people and often suffer from other general or ophthalmologic diseases. Therefore, the best option is to perform an accurate ophthalmological examination before starting chemotherapy. It will help to exclude other pre-existing ocular diseases and distinguish those ocular symptoms, which are caused by chemotherapeutic agents.

Diabetic retinopathy and diabetic macular edema are the main complications of poorly-controlled diabetes [36]. Cystoid macular edema is also one of the side effects of a retinal vein occlusion, which may occur in patients with the risk factors such as hypertension or hyperlipidemia [37]. Symptoms of cystoid macular edema like metamorphopsia, decreased visual acuity, scotomas regardless of the cause are identical. Only a full ophthalmologic examination (including additional tests, especially fluorescein angiography), and the comparison between current results to the study conducted before chemotherapy will help to find an exact cause of the disorder. Physicians need to implement the treatment according to the diagnosis. For example, if the cystoid macular edema is a complication of retinal vein occlusion it is necessary to give the patient an anti-VEGF drug (aflibercept, ranibizumab or bevacizumab) and in CME due to taxane-based chemotherapy cessation of therapy is sufficient.

Optic neuropathy might be a potential side effect of taxane-based chemotherapy, or the changes in the optic nerve may be caused by pre-existing undiagnosed glaucoma. Optic disc evaluation, nerve fibers and retinal ganglion cells assessment using optical coherence tomography (OCT), visual field test, intraocular pressure measurement, and in some cases, electrophysiological examination will help to diagnose the patient.

Also, that excessive tearing may be the result of previous injury, surgery in the nose or sinuses, as well as a symptom of a granulomatous disease like sarcoidosis or granulomatosis with polyangiitis.

SUMMARY

Physicians taking care of patients during chemotherapy based on taxanes, as well as on every other cytostatic medicine, should be aware of these probable ocular complications. An early diagnosis of ophthalmic complications caused by chemotherapy makes it possible to avoid long-lasting adverse effects.

Table 1. Possible ocular side effects of the taxane-based chemotherapy.

	POSSIBLE OCULAR SIDE EFFECT
Paklitaxel, nab-paklitaxel	optic neuropathy
	photopsia, scintillating scotoma
	decreased visual acuity
	blurry vision
	visual field defects
	cystoid macular edema (CME)
Docetaxel	lacrimal punctum and/or lacrimal canal obstruction
	excessive tearing (epiphora)
	optic neuropathy
	papilledema
	cystoid macular edema (CME)
Cabazitaxel	optic neuropathy
	decreased visual acuity
	colour vision deficiency
	visual field defects

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